Inflammatory disorders of the small intestine and large bowel

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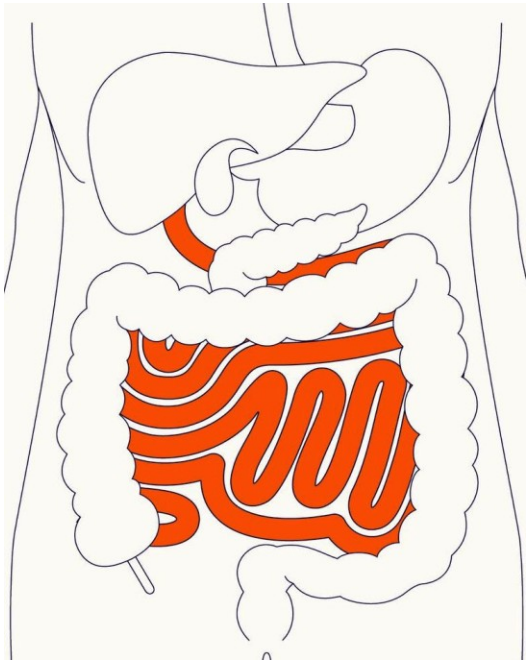
Case presentation

History and physical exmination	Investigations
34 year old female presents with a 12-month history of **vague abdominal symptoms** (bloating and occasional loose stools) Feels **tired and has migraines** Suffers from **joint discomfort** (spine, hips and knees) No personal or family history of IBD or autoimmune diseases No history of abdominal surgery	Hemoglobin (10.2 g/dL) MCV (72 fL) Serum Iron (30 µg/dL) Ferritin (8 ng/mL) No improvement on oral iron treatment Serology shows slightly raised tTG-IgA (2x normal) and total serum IgA is normal Endoscopy and duodenal biopsy planned

AI offered interpretation

- Symptoms align with celiac disease
- Labs suggest malabsorption (hallmark of celiac disease)
- Serology supports celiac disease in this context
- Endoscopy with duodenal biopsy (gold standard) is essential
- Histology would be definitive



Celiac disease

Exposure to dietary gluten

⬇

Genetically susceptible individuals

⬇

Abnormal immune response

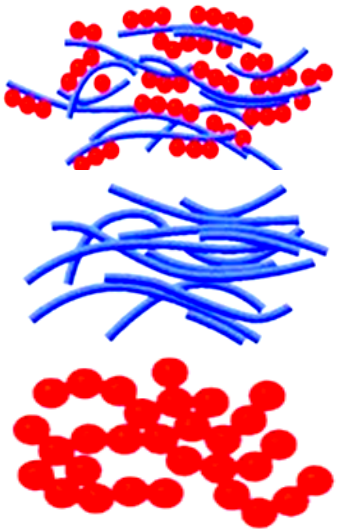
⬇

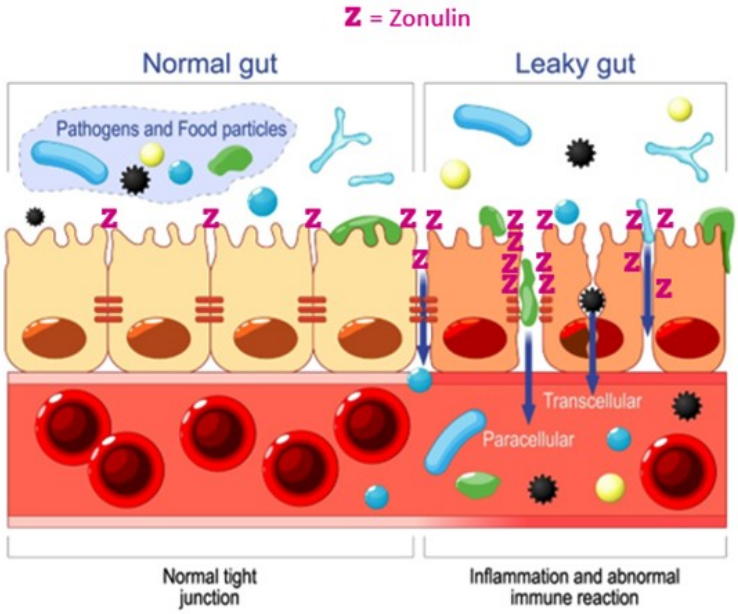
Small bowel mucosal injury

⬇

Malabsorption and steatorrhea in adults

Failure to thrive in children





Gluten

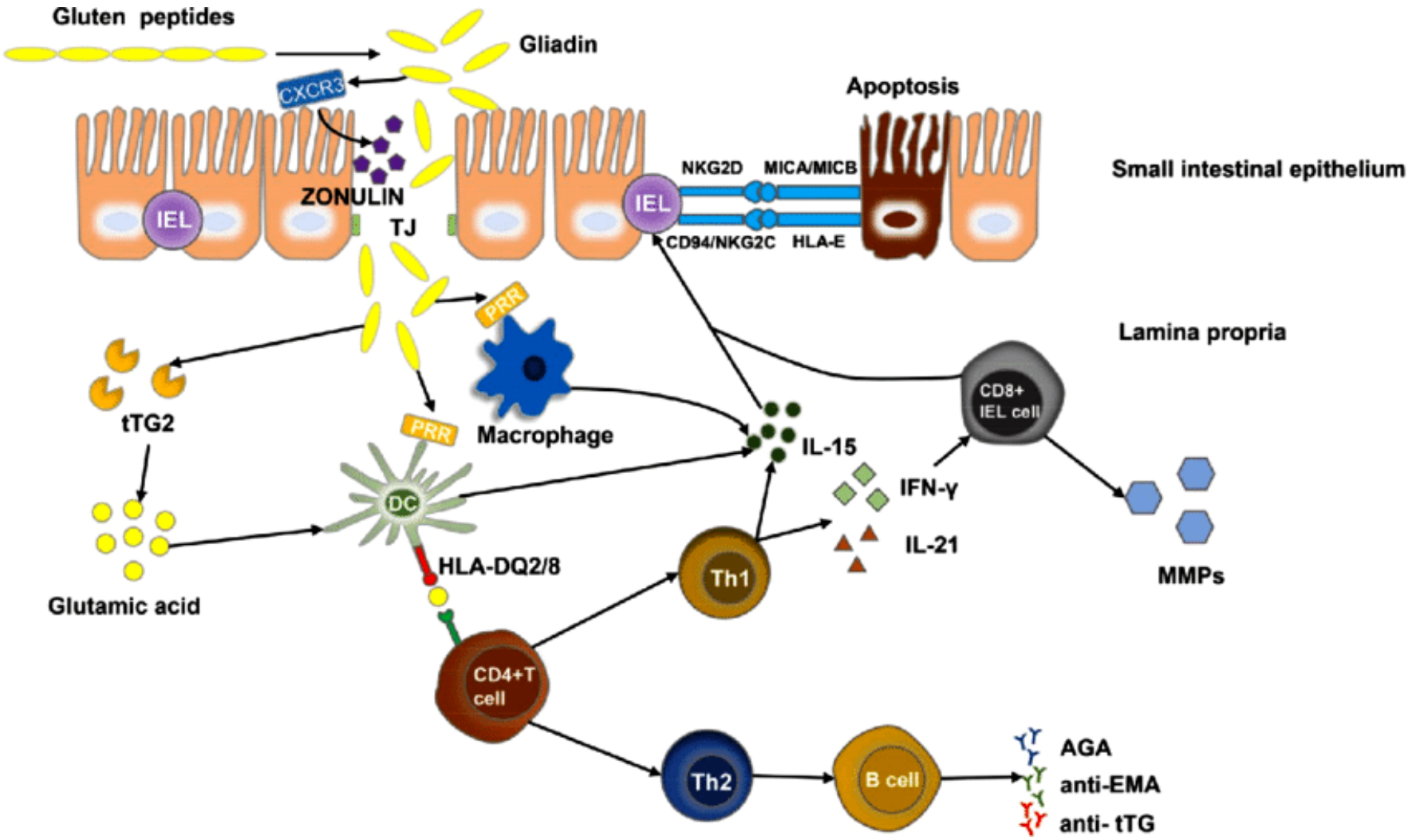
Gluten is a **very large protein** (molecular weight of 3000 kD) found in wheat, barley and rye and food made from them

Glutenin (~47%) is a fibrous protein, rich in cysteine and acts as binder and thickener of food and is responsible for the elastic texture of the dough and firmness of the bread

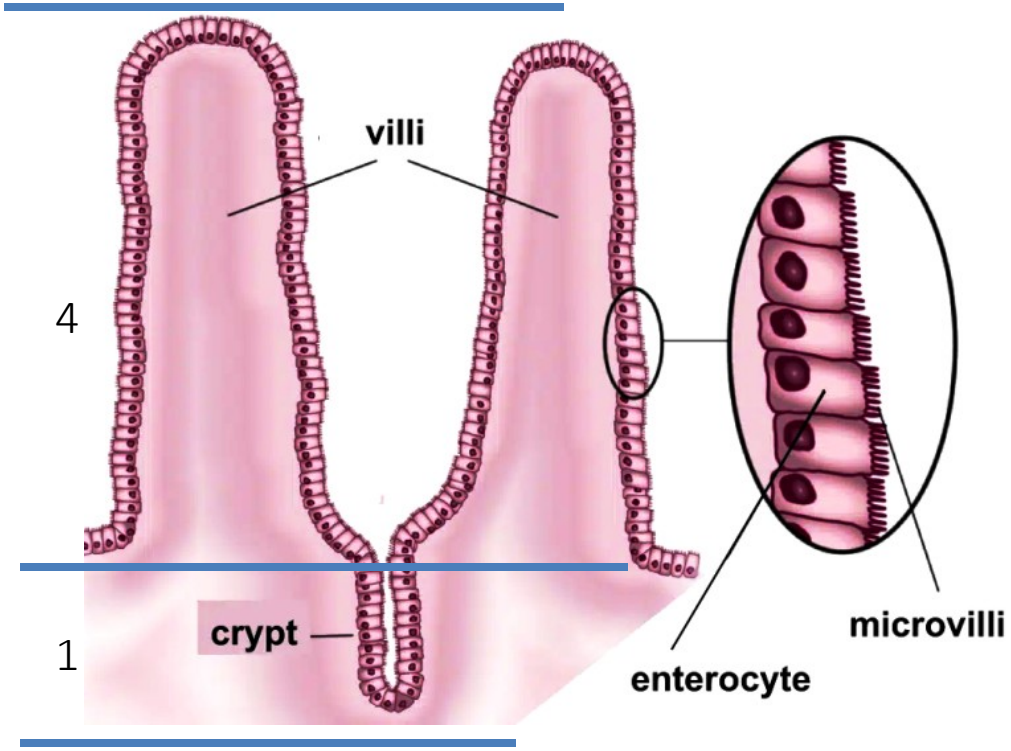
Gliadin (45%) is a globular protein, rich in **proline and glutamine and is resistant to digestion** (not absorbed in normal people (pass out of the body in faeces)

Increased intestinal permeability in CD patients allows these peptides to be absorbed

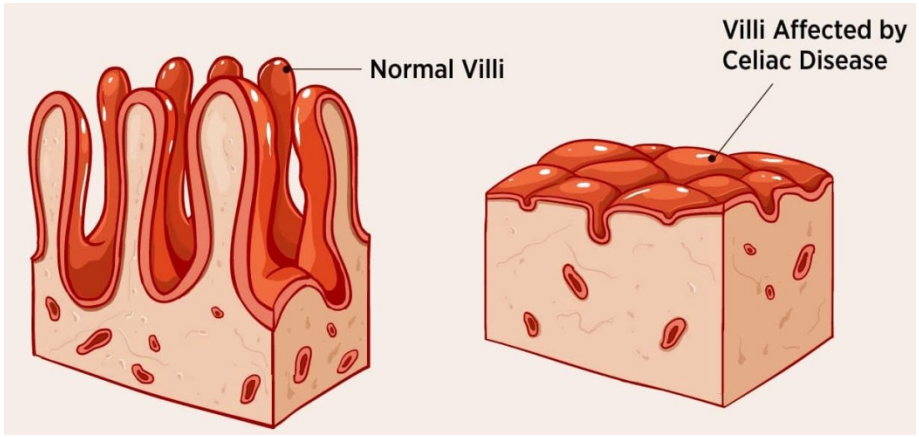
Pathogenesis of celiac disease



Pathogenesis of celiac disease	
Surface epithelium	Gliadin interaction with intestinal epithelial cells and causes **Zonulin overexpression**
Lamina propria	Excess Zonulin leads to **increased intestinal permeability** which allows **Gliadin to reach lamina propria**
	Tissue transglutaminase (tTg) deaminates gliadin and binds it to **HLA-DQ2 and HLA-DQ-8** which is recognized by **Antigen Presenting Cells (APC)**
	APC activates **T helper (CD4) cells** to release cytokine **(IFγ, TNFα and ILs) and recruit cytotoxic (CD8) T cells and macrophages and stimulate B cells to produce autoantibodies**
	Cytokines and CTLs (CD8 cells) cause intestinal damage (loss of villi, inflammation and compensatory crypt hyperplasia)
Loss of absorptive surface causes **maldigestion and malabsorption** and the associated inflammatory damage further **increase permeability** of the lining leading to **diarrhea**	



Villous : crypt ratio = 4:1

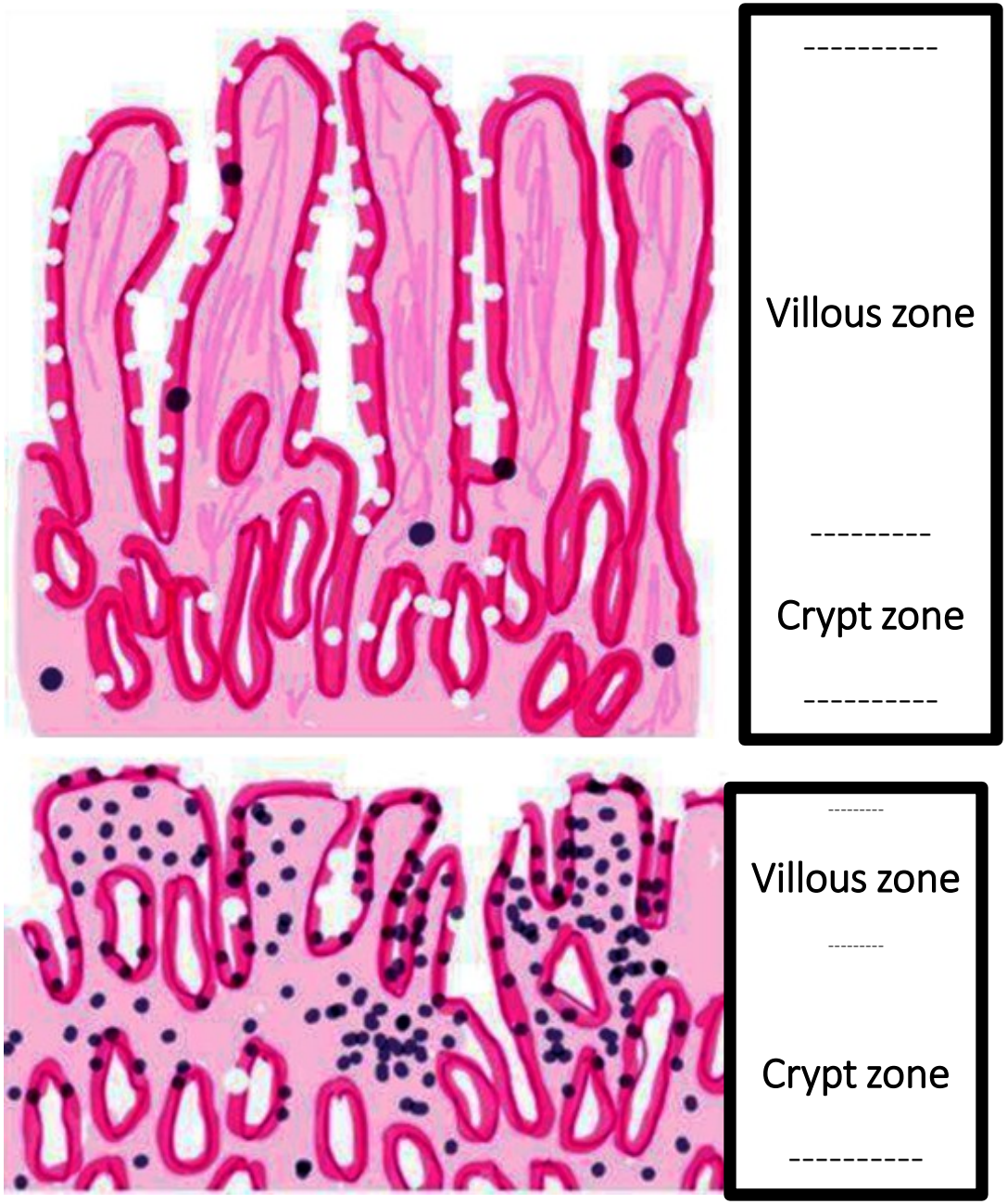


Surface area of a small bowel (cylinder 6 meters long and 2.5 cm in diameter) is <1 square meters

Absorptive surface area of normal small bowel is thousands of times larger greater than 1 square meter

Absorptive surface area of small bowel in celiac disease is markedly reduced due to epithelial damage and flattening of villi and loss of microvilli

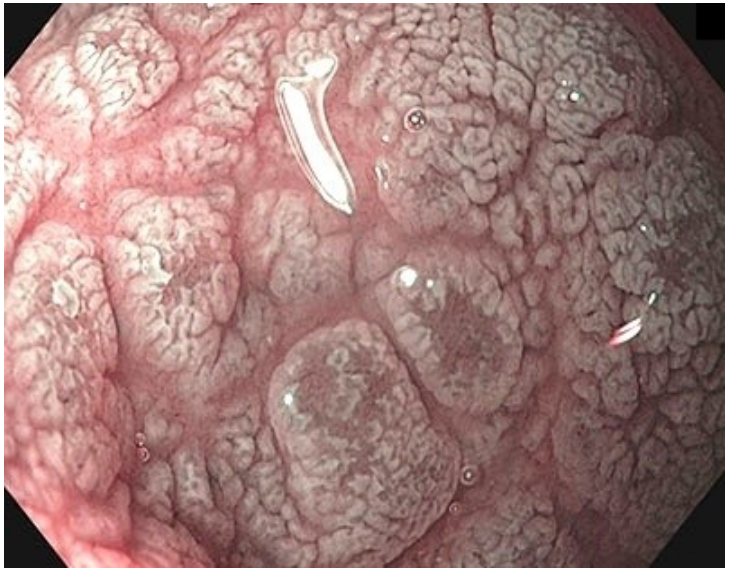
Loss of absorptive surface causes maldigestion and malabsorption of nutrients and the associated inflammatory damage increase permeability of the lining leading to diarrhea



Normal small bowel mucosa
Villous to crypt ratio >4:1

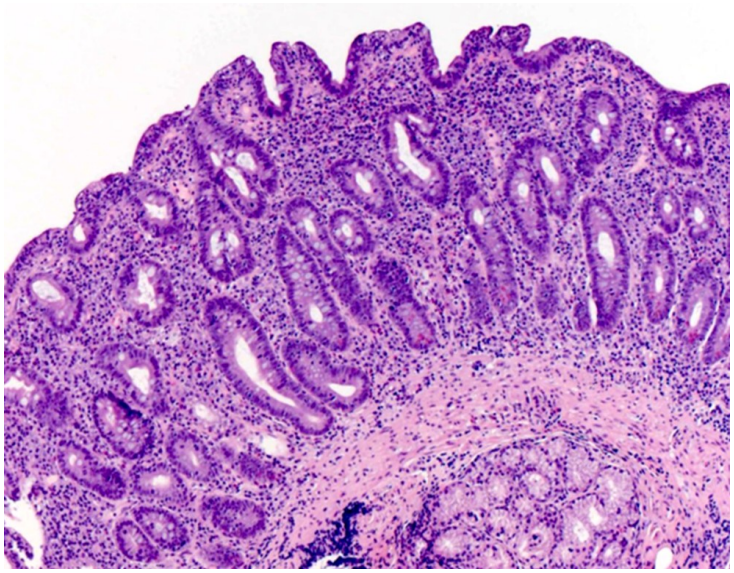
Celiac disease small bowel mucosa
Villous to crypt ratio <1:4

Normal

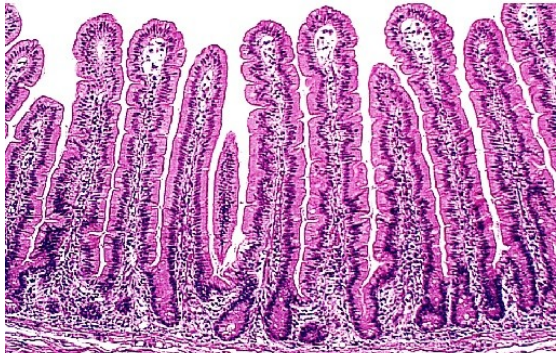


Celiac Disease

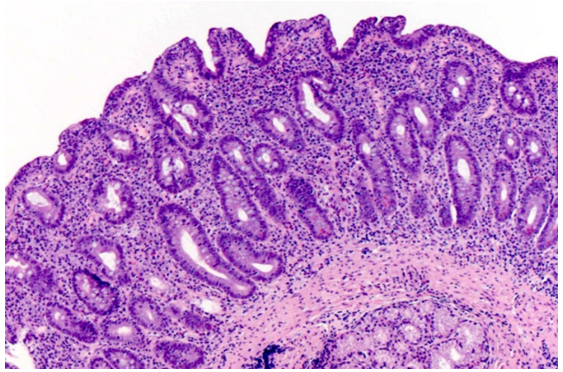
Normal



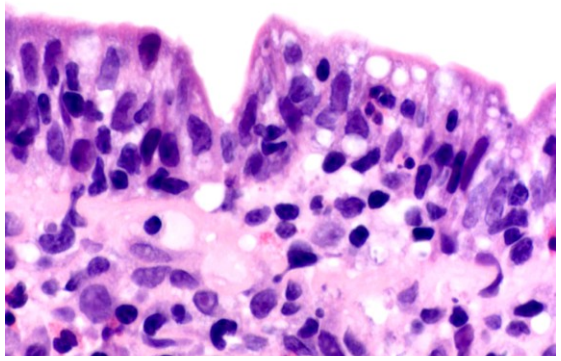
Celiac Disease



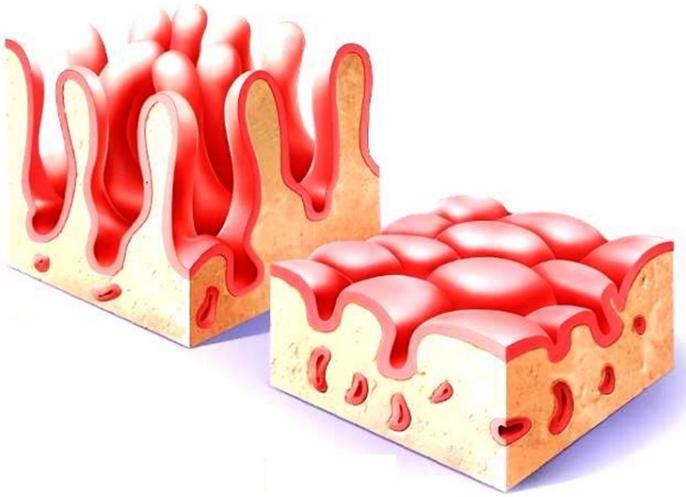
Normal Jejunum



Celiac Disease



Intraepithelial lymphocytosis and epithelial cell damage



Histology of celiac disease

Loss of villi (villous atrophy)

Crypt hyperplasia

Chronic inflammation

Intraepithelial lymphocytosis

Surface epithelial cell damage

How is CD diagnosed?

Serology

Anti-transglutaminase antibodies (TG), anti-endomysium antibodies (EMA), antibodies against deaminated gliadin peptides (DGP) or anti-gliadin antibody (AGA)

Histology

Villous atrophy, crypt hyperplasia, surface intraepithelial lymphocytosis, chronic inflammation, and surface epithelial damage

Response to GFD

Dramatic response to Gluten Free Diet

Gluten challenge

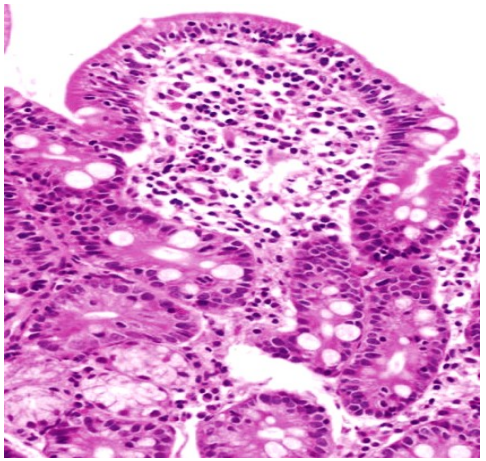
Instillation of gluten (wheat, barley or rye) into the small bowel of CD patients has been shown to flatten mucosa in about 12 hours and their regeneration in 48 hours

Grading villous atrophy in CD

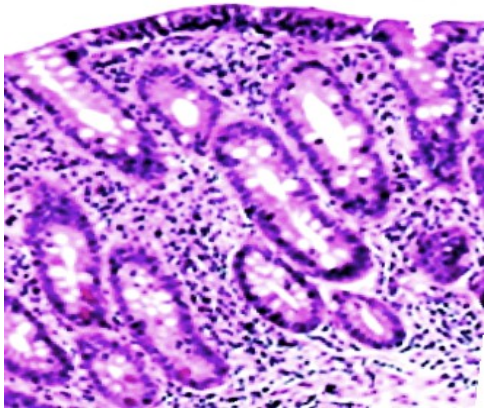
Normal

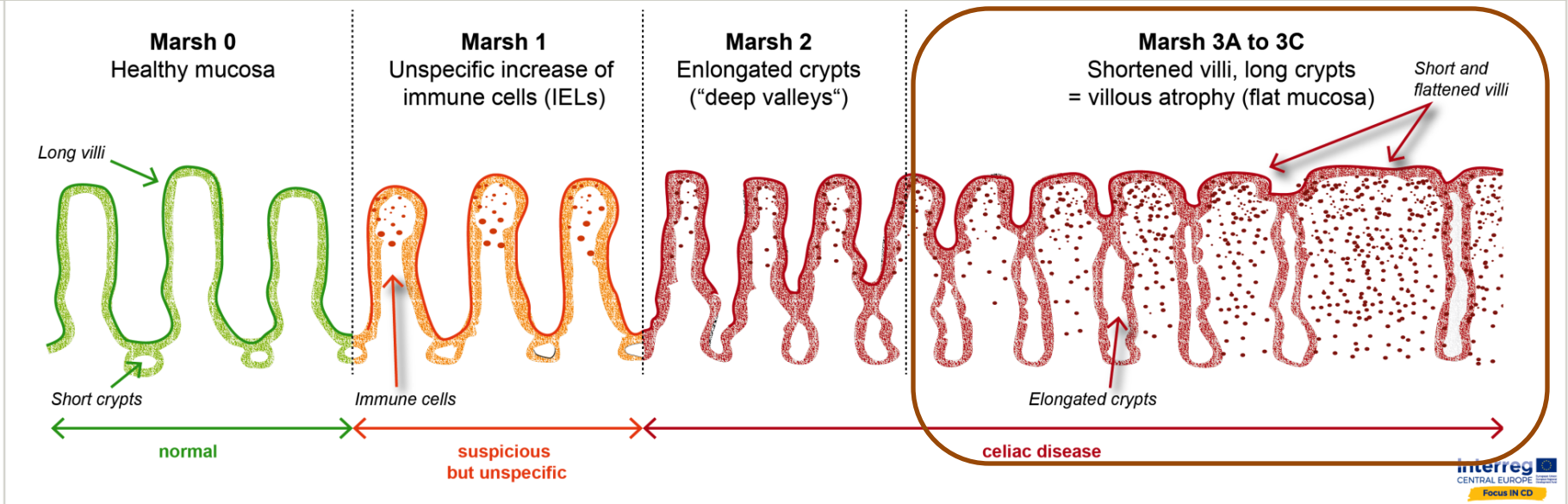
Partial villous atrophy

Subtotal villous atrophy



Total villous atrophy

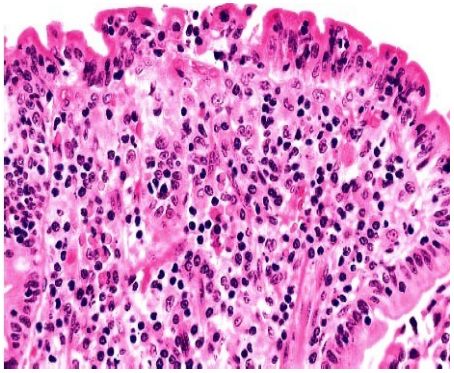




Type	Definition
0	Normal duodenal biopsy
I	Normal mucosal architecture with increased intraepithelial lymphocytes
II	Hyperplastic crypts, but near normal villi
IIIa	Hyperplastic crypts with partial villous atrophy
IIIb	Hyperplastic crypts with subtotal villous atrophy
IIIc	Hyperplastic crypts with total villous atrophy

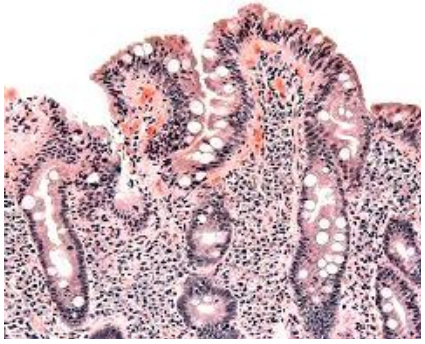
Michael Marsh
1937-2021

Histological differential diagnosis of celiac disease



Intraepithelial lymphocytosis

Crypt hyperplasia



Villous atrophy

Villous atrophy + crypt hyperplasia + intraepithelial lymphocytosis = Celiac disease in appropriate clinical setting

Increased IELs	*Crypt Hyperplasia*	*Villous abnormalities*
Celiac disease	Chronic bacterial infections	Celiac disease
Bacterial infections	Chronic viral infections	Tropical sprue
Viral infections	Chronic parasitic infections	Crohn's disease
Parasitic infestations	Chronic fungal infections	Nutritional deficiencies
Fungal infections	Non-steroidal anti-inflammatory agents	Micro-villous inclusion disease
Non-steroidal anti-inflammatory agents	Drug-induced changes	Tufting enteropathy
H pylori gastritis and duodenitis	H pylori infection	Giardiasis
Giardiasis	Chronic Giardiasis	Autoimmune enteropathy
Autoimmune enteritis	Autoimmune enteritis	Graft versus host disease
Crohn's disease	Crohn's disease	HIV and AIDS
Common variable immunodeficiency	Common variable immunodeficiency	Common variable immunodeficiency
Tropical sprue	Celiac disease	Giardiasis
Intestinal lymphomas	Tropical sprue	Immune proliferative SI disease
Other medications, as Olmesartan, oral contraceptive pills, etc	Gastric juice induced chronic inflammation	Other SI lymphomas
		Other medications, as Olmesartan, oral contraceptive pills, MMF, Methotrexate, immune checkpoint inhibitors, Azathioprine, etc

How many biopsies should you take?

Nature of mucosal changes in CD

Mucosal damage in CD is often **focal/patchy**

Proximal duodenum is most severely injured and may be the only injured area

Biopsy

Duodenal bulb

Distal duodenum

Any endoscopic abnormality

Children

Biopsy may not be necessary in children with

- Antibodies to tTg >10 than normal
- HLA (DQ2 and DQ8) genotypes

Serology

Not always straightforward

Seronegative CD is underestimated

2 duodenal biopsies will suggest celiac disease in 100% and confirm CD in 90%

4 duodenal biopsies will diagnose celiac disease in 100% of the cases

(Pais et al 2008)

When to re-biopsy

No need to re-biopsy

Clinical response to dietary gluten exclusion

Re-biopsy may cause confusion

1. Focal and patchy nature of CD
2. Proximal small bowel improvement may lag behind the more rapid healing in the distal part (jejunum)

Re-biopsy if the patient

1. Fails to respond to a GFD
2. Relapses while on a GFD

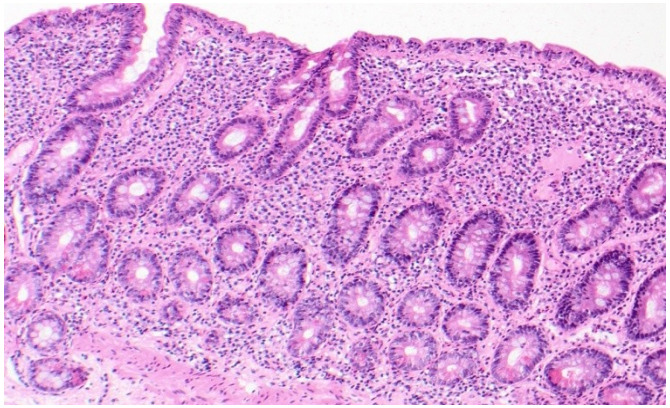
Treatment failure in celiac disease

Major cause is dietary lapse or inadvertent consumption of gluten

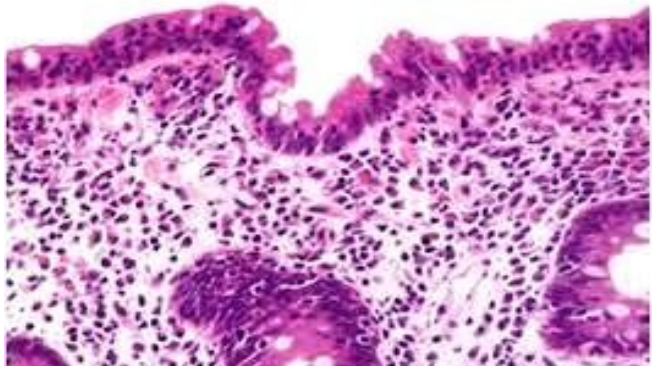
A small subset of patients do not respond GFD and these rare patients may have another disease (incorrect diagnosis)

An alternate consideration is disease progression

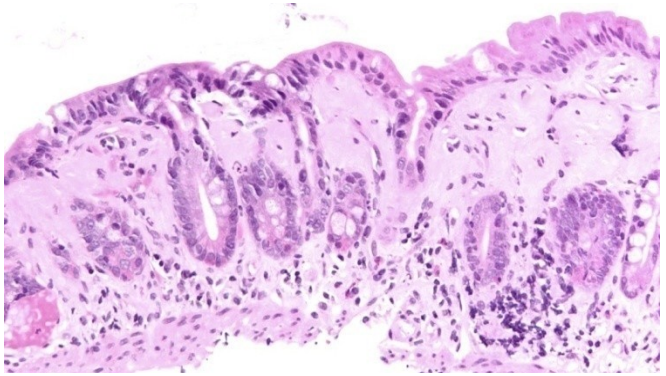
Recurrence or worsening of symptoms in a successfully treated patient may herald development of a malignancy (lymphoma)



Celiac disease



Tropical Sprue



Collagenous Sprue

Celiac complications

Refractory CD

Symptom persistence and abnormal biopsy after at least **1 year on a strict GFD, confirmed by negative CD serology** reported in 1% of total cases

- Type 1, where the IEL population has a normal **(non-clonal)** $CD3^+CD8^+$ phenotype
- Type 2, with **a clonal rearrangement** of the gamma-chain of the T cell receptor

Intestinal lymphoma

>10 time higher than in the general population for **T cell lymphoma** and to a lesser extent for B cell lymphoma

Lymphoma follows RCD (50% in type 2 RCD and in 15% in type 1 RCD over 5 years)

Small bowel adenocarcinoma

More common than in the general population (OR ranging between 4.3 to 60.0); usually being detectable in the **jejunum**

Main clinical types of CD

Classic CD

Malabsorption and steatorrhea in adults

Failure to thrive in children

Atypical CD

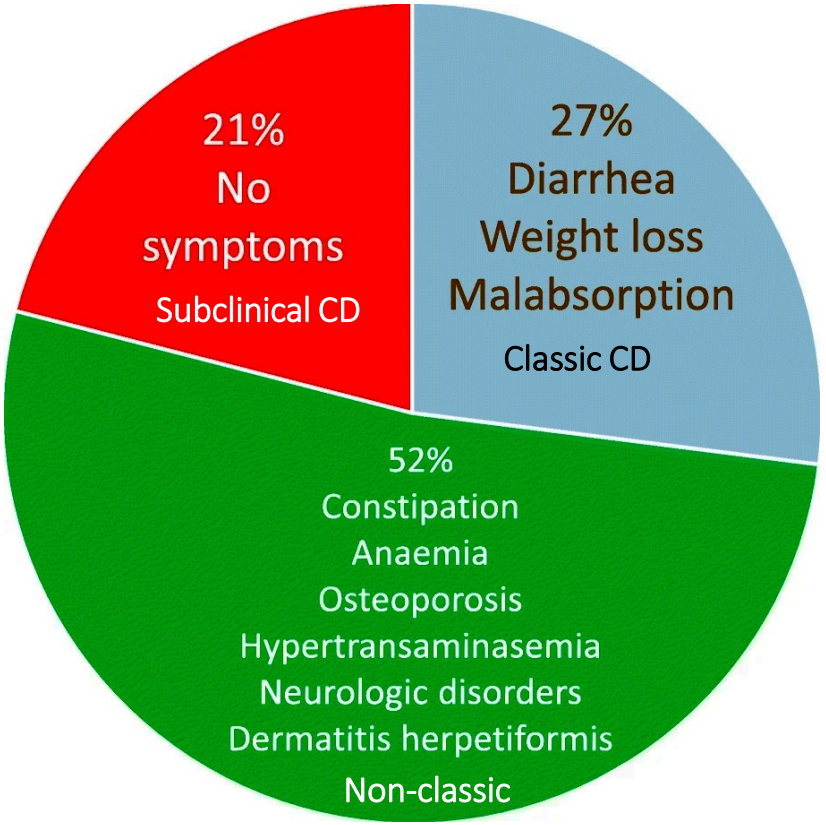
Lacks overt steatorrhea

Latent CD

Biochemical disease

Refractory CD

Unresponsive to strict GFD diet



How common is celiac disease?

Prevalence of CD, based on malabsorption and steatorrhea in adults and failure to thrive in children is about 1 in 3000 (0.003%)

Using population-based serology, that figure is at least 1%

Recent data indicates the figure might be closer to 2%

Wide regional differences (Germany 0.3%, Finland 2.4%)

Tropical sprue

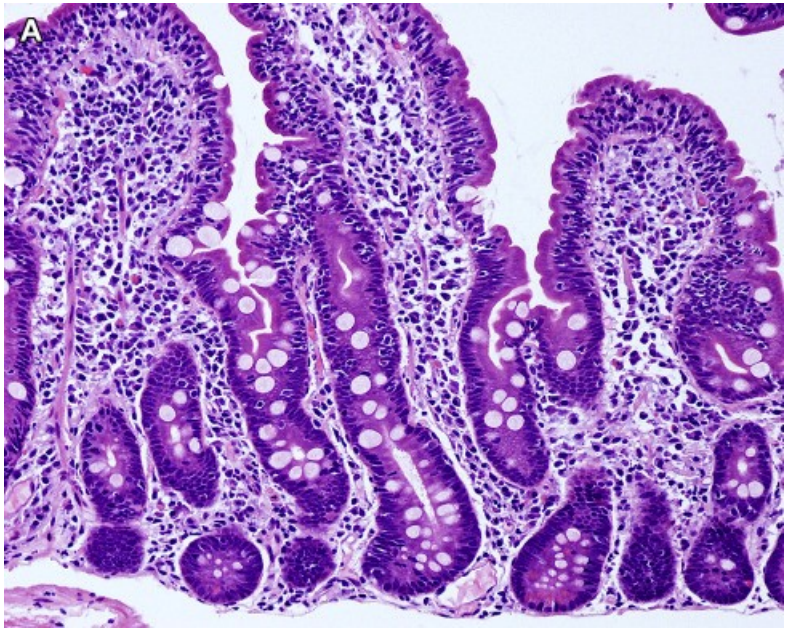
Chronic diarrheal disease with pale stools, abdominal cramps, nausea, vomiting, loss of appetite, fatigue and weight loss, likely due to an infection

Tropical areas within 30° latitude of the equator, especially in Asia and the Caribbean

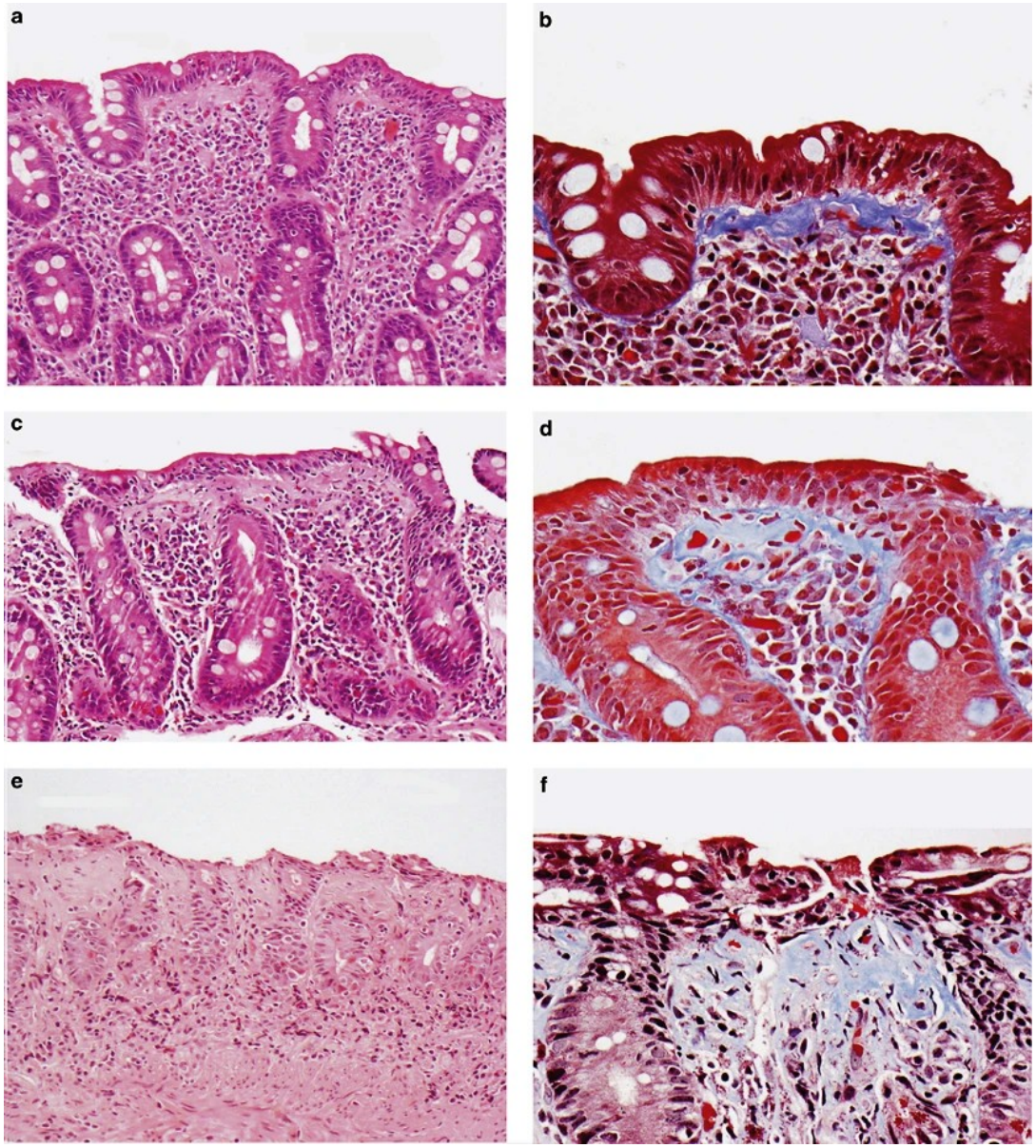
Treated with antibiotics, nutritional supplements and vitamin B12 and folic acid

Histology of tropical sprue

Diffuse uniform mucosal change
Total villous atrophy is rare
Intraepithelial lymphocytosis is light
Negative celiac serology



TS	CD
Diffuse mucosal injury	Focal or patchy mucosal injury
Uniform villous atrophy	Variable villous atrophy
Light intraepithelial lymphocytosis	Heavy intraepithelial lymphocytosis
Negative serology	Positive serology



Collagenous sprue (CS)

Severe malabsorptive disorder

Not always gluten responsive

Thickened basement membrane and subepithelial collagen plate (>10 µm)

Cause is unknown

No standardized therapy but treated with GFD, corticosteroids

Complications (small bowel ulceration, perforation, lymphoma)

Diagnosis is based on clinical picture and pathologic findings

Autoimmune enteropathy (AIE)

Affects mainly **infants** in the first six months of life

Intractable **diarrhea**

No response to dietary changes

Autoantibodies (anti-enterocyte, anti-smooth muscle, anti-endoplasmic reticulum, anti-mitochondrial, anti-parietal cell, well as anti-DNA and antinuclear antibodies)

Other autoimmune issues and immunodeficiencies

Can be associated with various **hereditary syndromes**

Autoimmune enteropathy (AIE)

Villous abnormalities (blunting, atrophy and crypt hyperplasia)

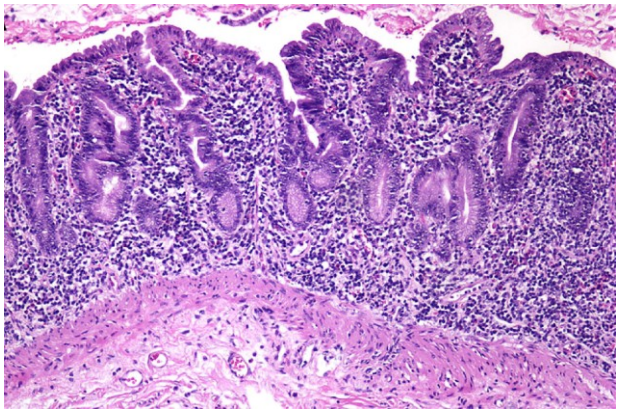
Diminished or absent **goblet cells**

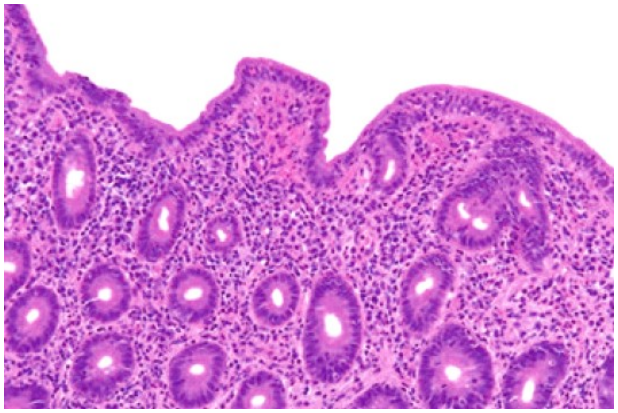
Inflammation (increased intraepithelial lymphocytes and active or acute inflammation and cryptitis)

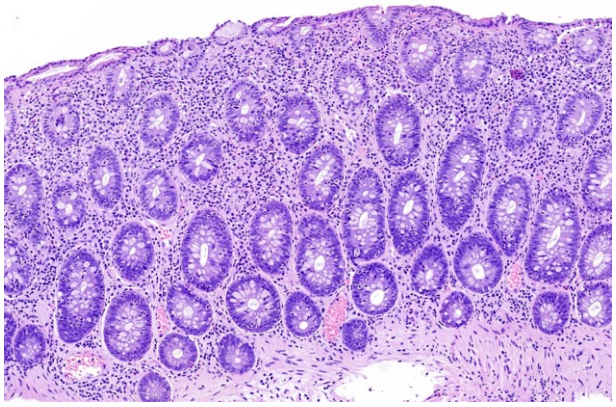
Increased crypt apoptosis akin to GVHD

Findings are **pronounced in the small bowel**; variable findings in **stomach and colon**

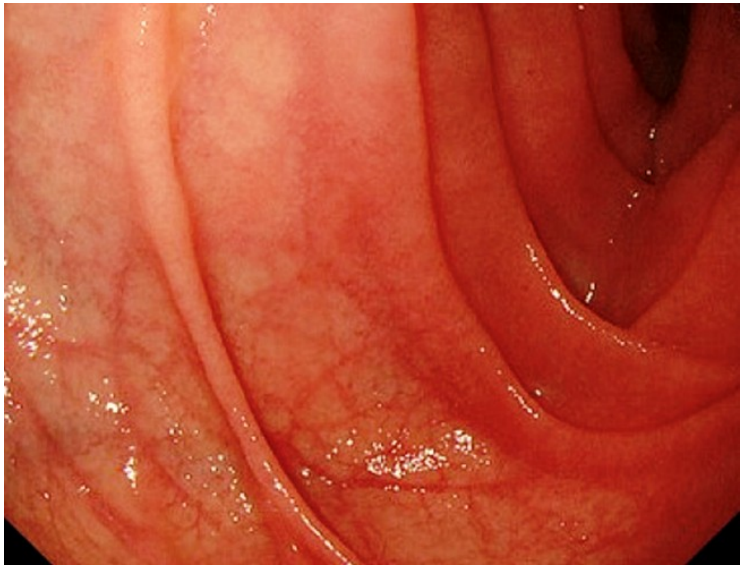
Severity of histological findings variable among individuals and **reversible with therapy**



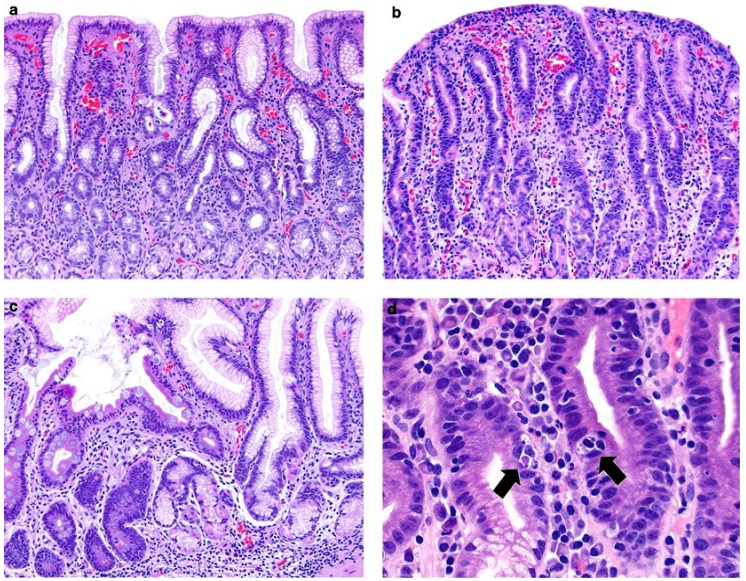




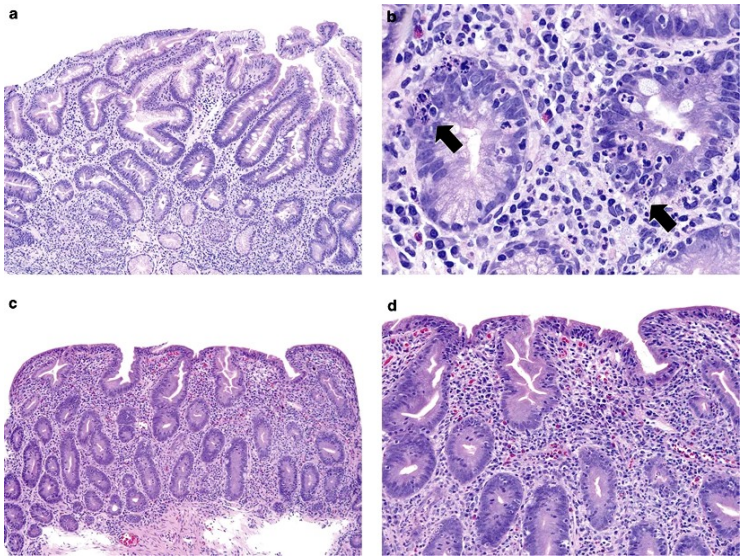
Autoimmune enteropathy (AIE)



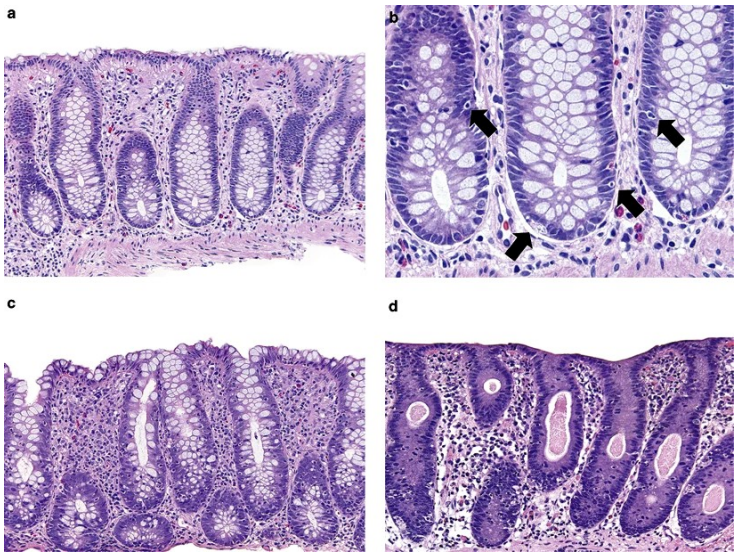
Duodenum



Stomach



Duodenum



Colon

Similarities and differences between celiac disease, gluten sensitivity and wheat allergy			
Disease	Celiac disease	Gluten sensitivity	Wheat allergy
Interval	Months to years	Hours to days	Minutes to hours
Pathogenesis	Autoimmunity	Innate immune response	Allergic response Type 1 (IgE)
HLA	DQ2 or DQ8 (97%)	DQ2, DQ8 or both (50%)	DQ2, DQ8 or both (30%)
Autoantibodies	Present	Absent	Absent
Enteropathy	Present	Variable	Absent
Pathology	Crypt hyperplasia villous atrophy intraepithelial lymphocytes	Slight increase in intraepithelial lymphocytes	Increased eosinophils in lamina propria
Symptoms	GI and systemic	GI and systemic	GI and systemic
Complications	Lymphoma (long-term)	No	Anaphylaxis (short-term)

Inflammatory disorders of the large intestine

Inflammatory Bowel Disease

Infectious colitis

Microscopic colitis

Drug induced colitis

Ischemic colitis

Other types

Case presentation

History and physical exmination	Investigations
A 55-year-old female with a **five-year history of fluctuating bowel habits** (alternating constipation and diarrhea) **Recent history of severe bloody diarrhea, cramping abdominal pain and weight loss** **NSAID and antibiotic use** for arthritis and worsening GI symptoms respectively **Previous colonic biopsy** revealed non-specific inflammation without a definitive diagnosis. Findings include **pyrexia, tachycardia, tachypnea, hypotension, and acute abdominal tenderness with distension**	**Marked leukocytosis, anemia, elevated CRP (95 mg/L) and ESR (75 mm/hr)** **Positive ANCA and ASCA antibodies** Stool analysis is positive for **C. difficile toxin.** Colonoscopy shows **superficial and deep ulceration with exudation.** **Histopathology** reveals mixed features, complicating definitive diagnosis

AI offered interpretation

Inflammatory Bowel Disease (IBD) with C. difficile Co-infection

Chronic history of fluctuating bowel habits, recent severe bloody diarrhea, weight loss, and systemic inflammatory response are highly suggestive of IBD (either Crohn disease or ulcerative colitis)

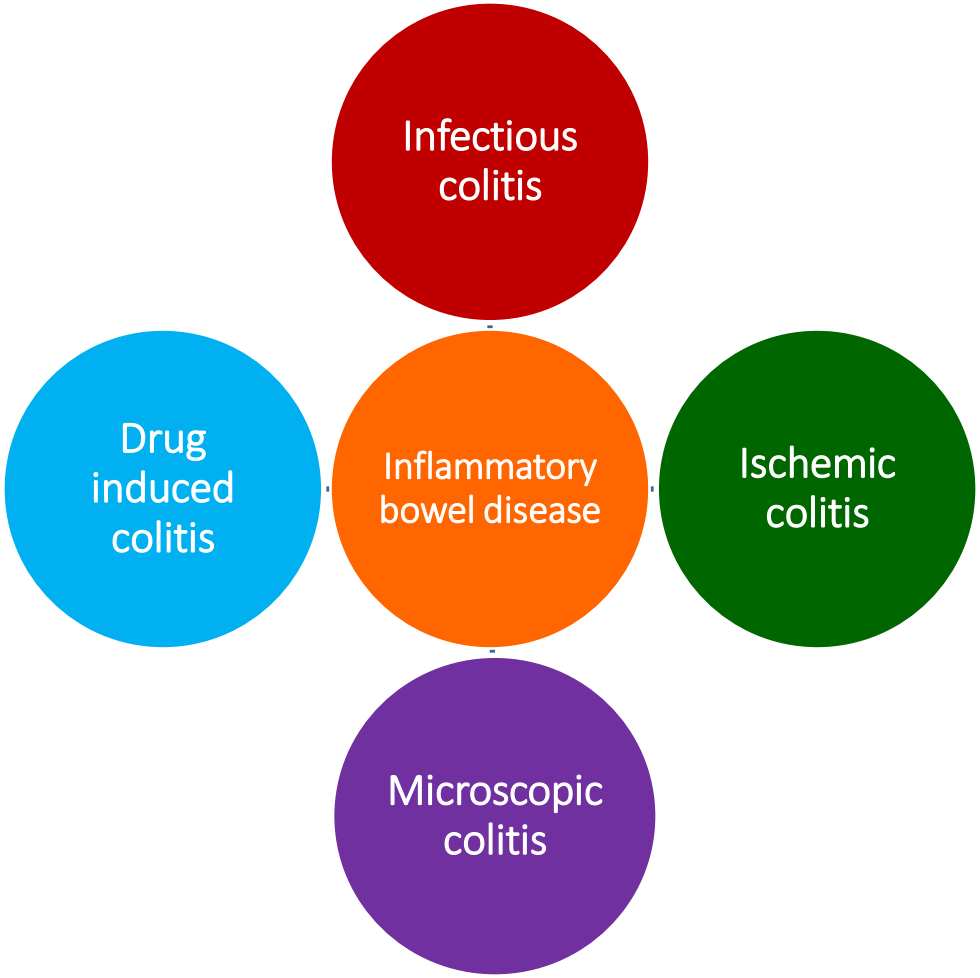
Presence of ANCA and ASCA antibodies further supports IBD

Positive C. difficile toxin indicates a superimposed infection, likely triggered by recent antibiotic use, which has exacerbated her symptoms

Integrated analysis of inflammatory diseases of the colorectum

Algorithms highlight the **most likely diagnosis**

No single algorithm can solve all the cases



Often multiple patterns are present in the same biopsy

Each case is unique and should be approached in the clinical context

Normal colorectal mucosa

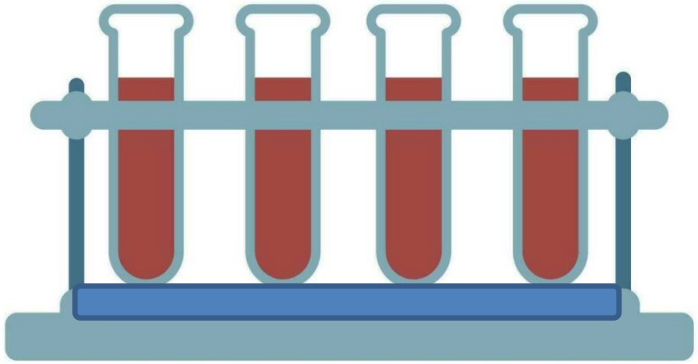
Crypts are lined with a single layer of simple columnar epithelium, rich in goblet cells

Crypts are straight (test tubes in a rack)

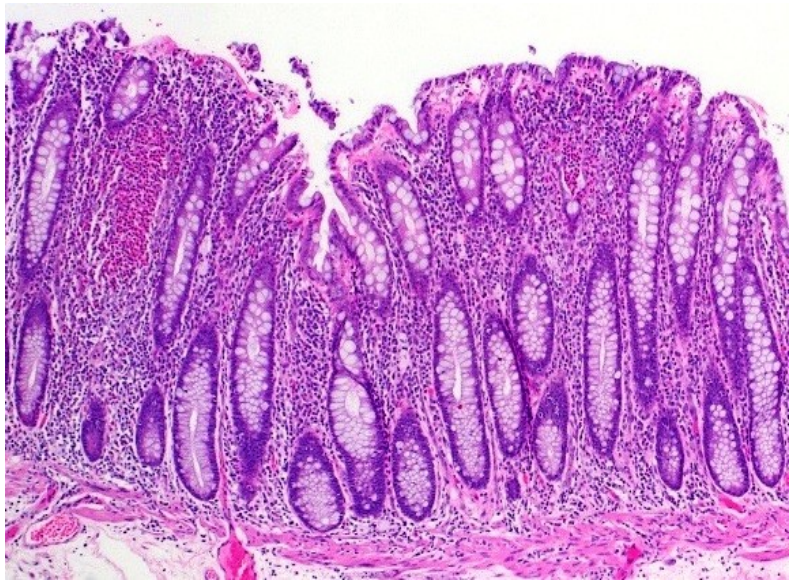
No crypt branching or distortion

Crypts almost touch the muscularis mucosae

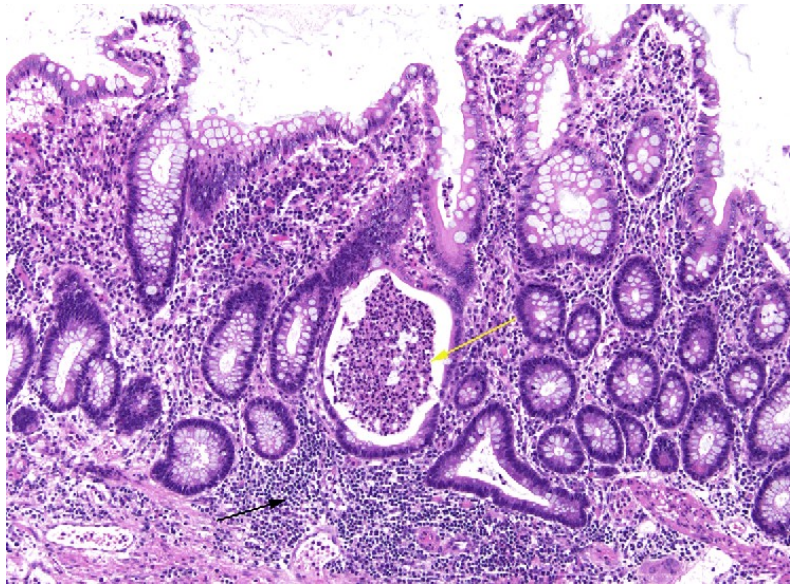
Lamina propria contains small numbers of lymphocytes, histiocytic and plasma cells



Acute (self limiting) versus chronic colitis		
	Acute	Chronic
Duration	Resolves in days	Persists for weeks, months or years
Etiology	Infections, toxins, drugs, ischemia, other conditions	Inflammatory bowel disease, microscopic colitis, drugs , other conditions
Morphology	Primarily neutrophilic Inflammation is most marked in the lamina propria with focal cryptitis and crypt abscesses	Primarily lymphoplasmacytic inflammation Epithelial damage (cryptitis, crypt abscess, crypt architectural distortion, atrophy), basal lymphoplasmacytosis, Paneth cell or pyloric metaplasia

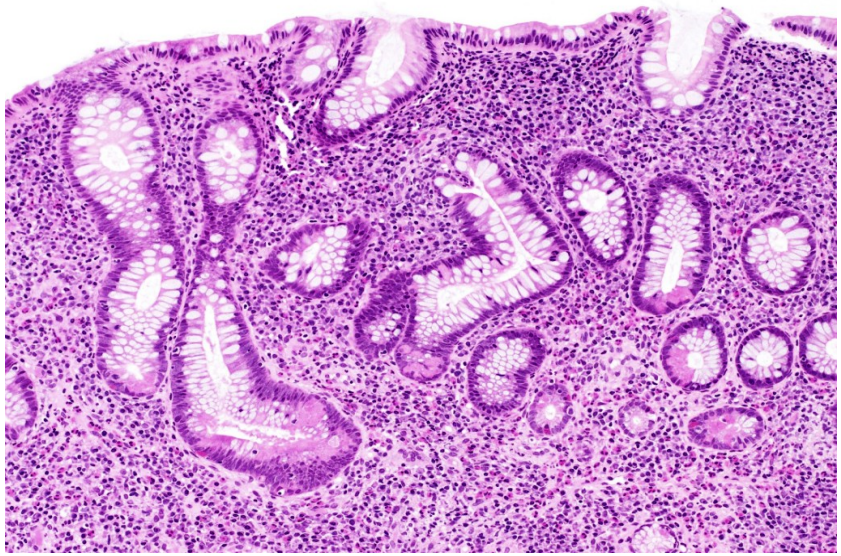


Acute colitis

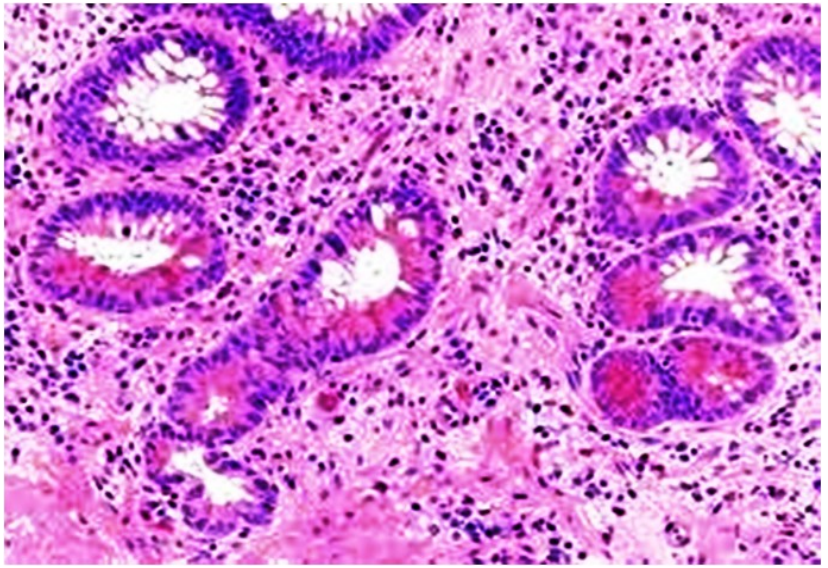


Chronic colitis

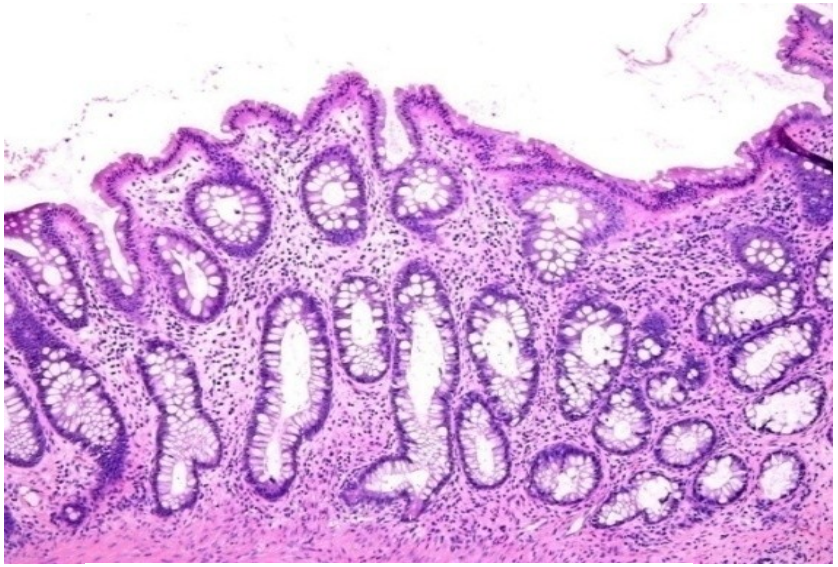
Signs of chronicity in inflammatory diseases of the colorectum



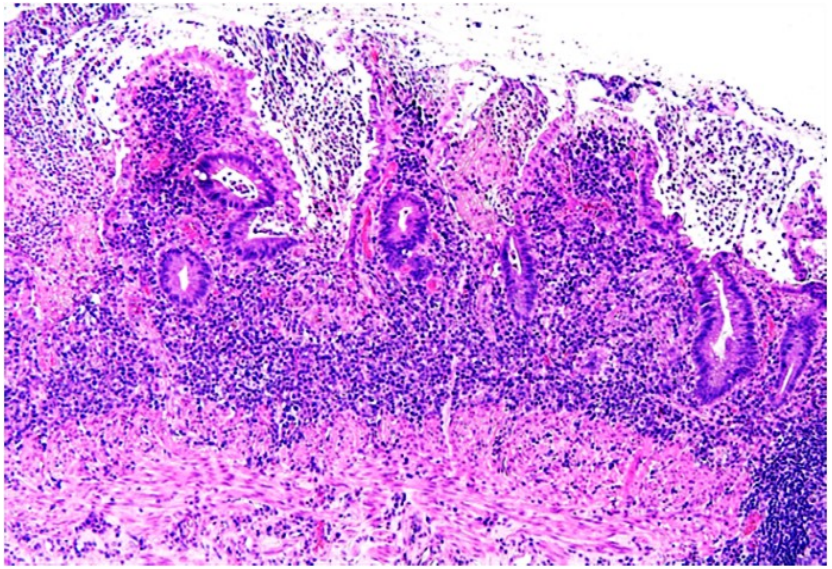
Distorted crypts-active



Paneth cell metaplasia



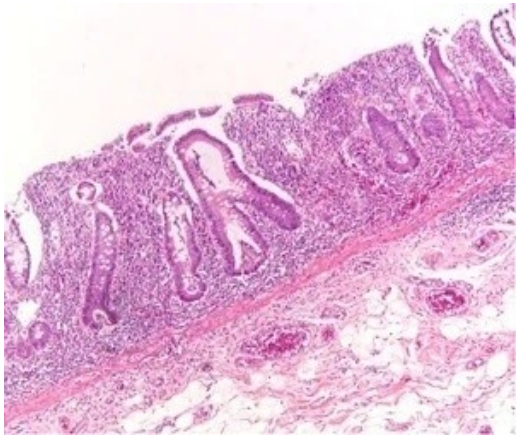
Distorted crypts-inactive



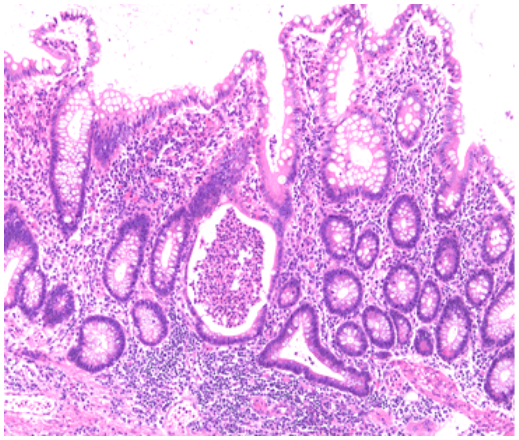
Basal lymphoplasmacytosis, atrophy & ulceration

I B D

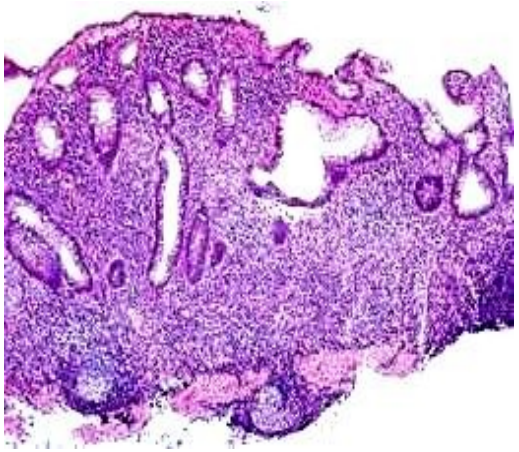
Approximately two thirds of IBD cases are UC, one third is CD and remainder are indeterminate or unclassified colitis



Ulcerative Colitis
Diffuse disease limited to the mucosa



Involvement of the rectum with proximal disease occurring in continuity with involved rectum



No skip lesions, fissures, fistulas, transmural inflammation or granulomas

Crohn Disease

Focal, patchy and transmural inflammation

Fissuring ulceration (cobble stoning)

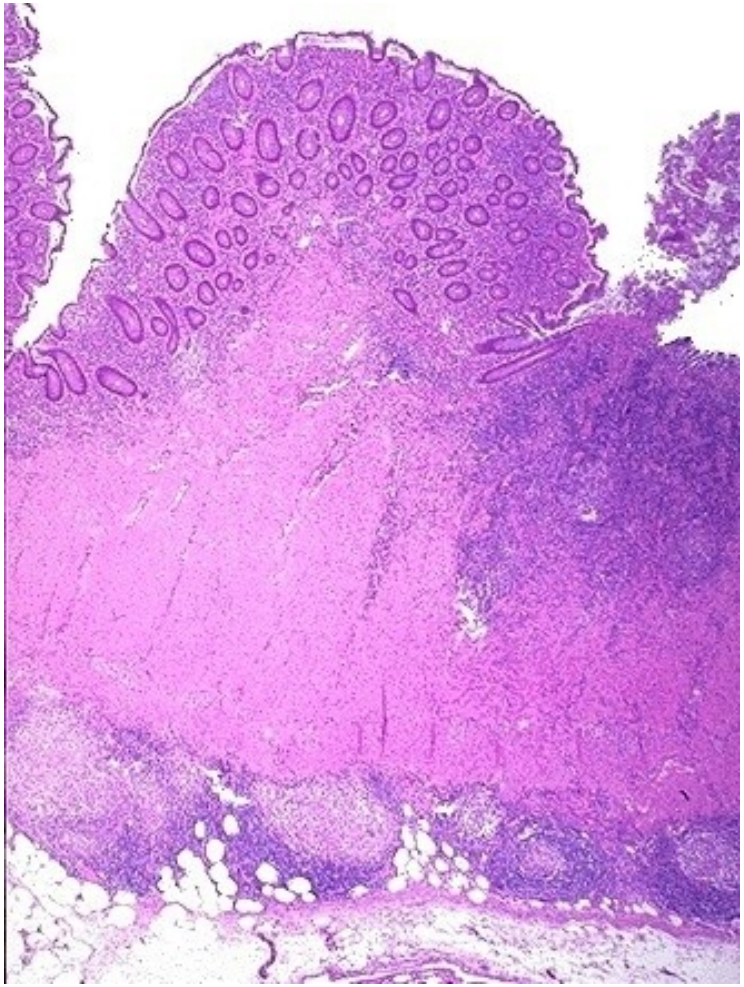
Granulomas

Lymphoid aggregate

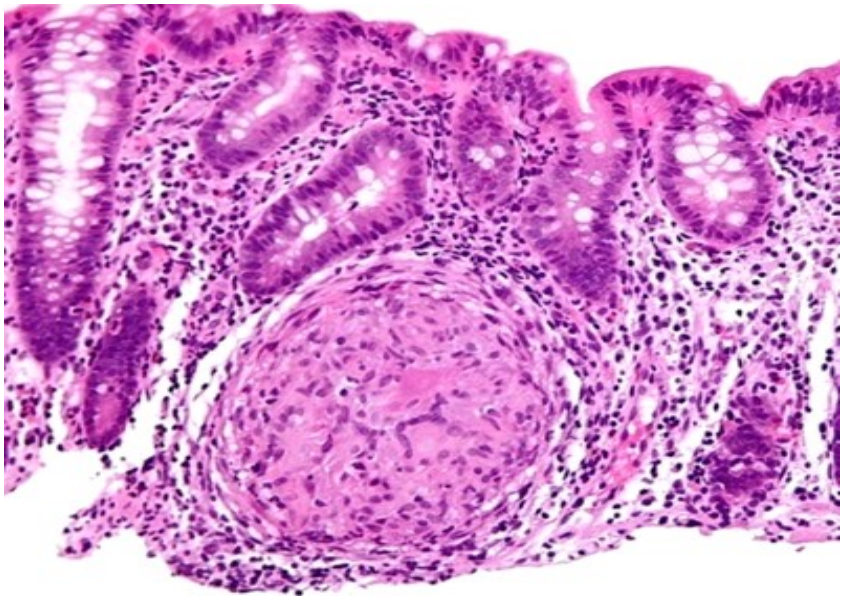
Scarring

Neural hypertrophy

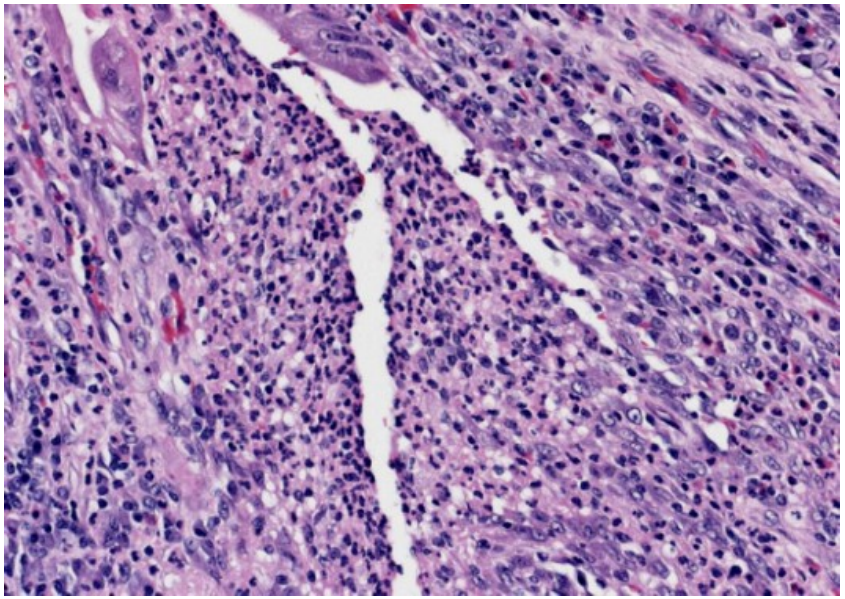
Crohn Disease



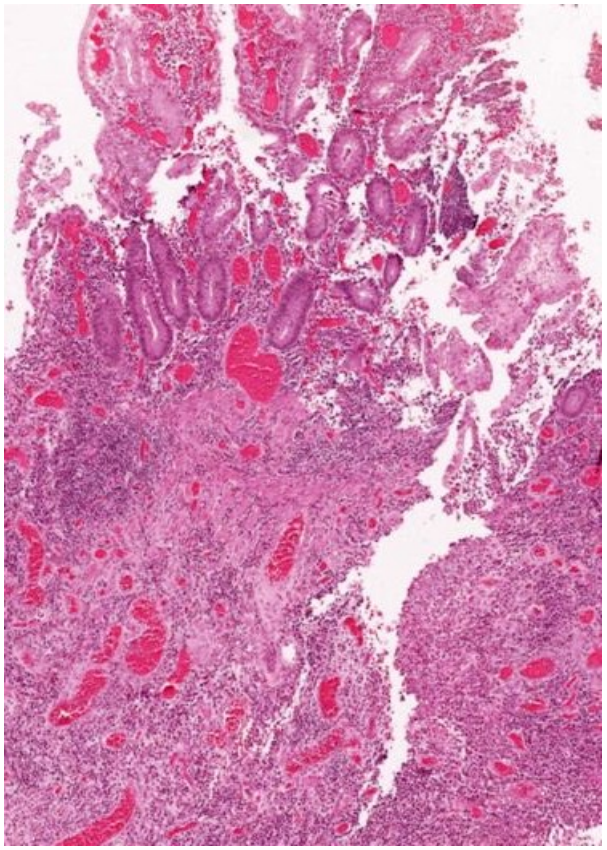
Transmural inflammation

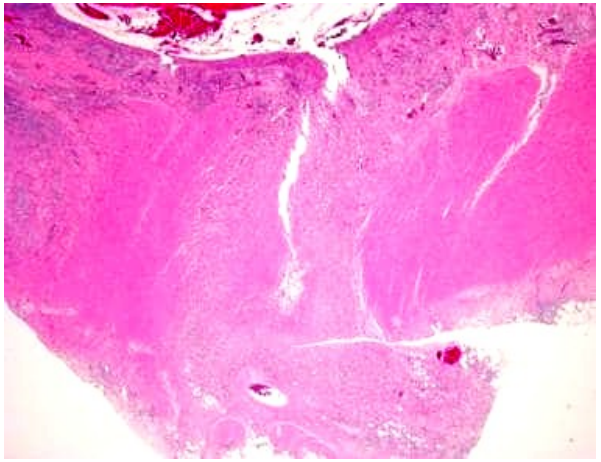


Granuloma



Fissuring

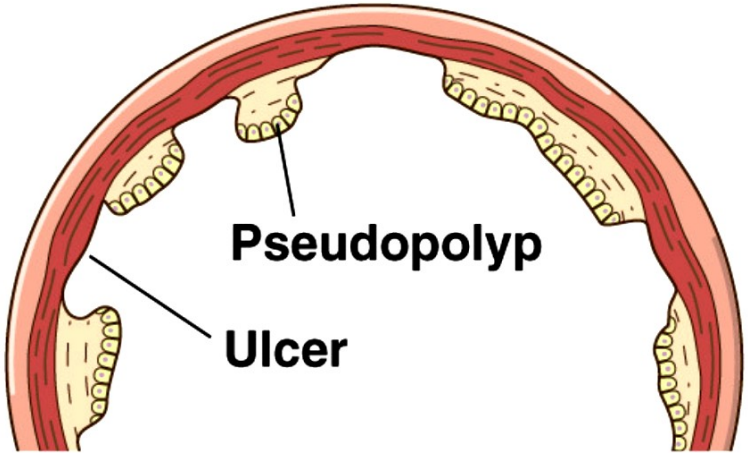


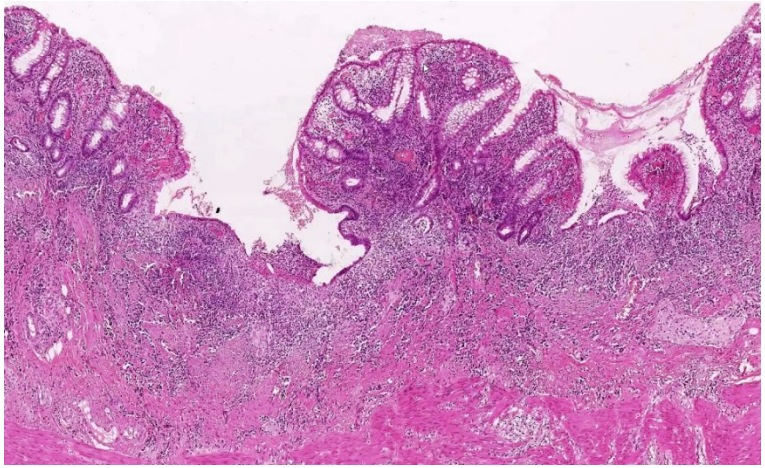


Crohn Disease

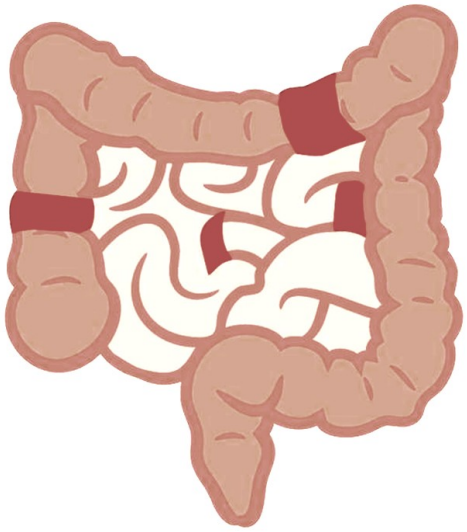
Ulceration

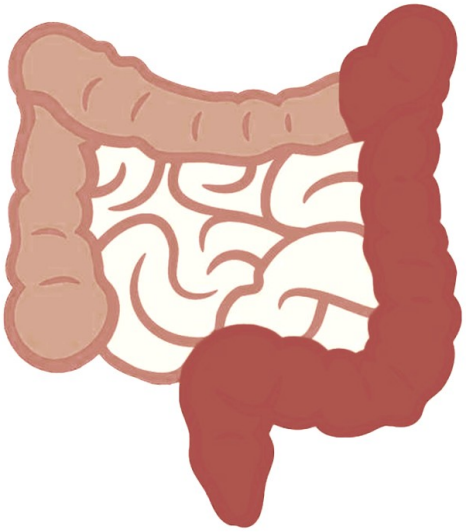
Fissuring





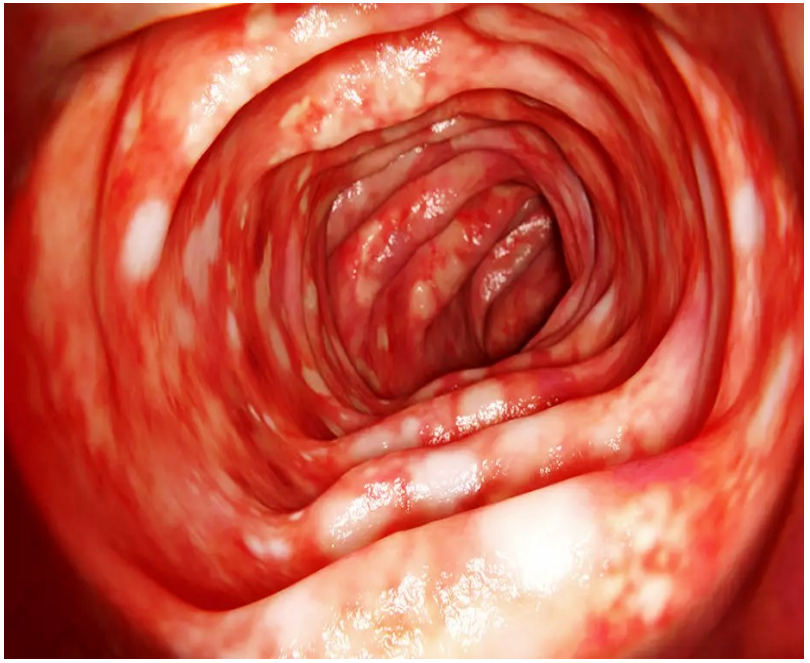
Inflammatory polyps in IBD
Result from cycles of injury and healing (ulceration, granulation tissue formation, inflammation, epithelial hyperplasia and fibromuscular proliferation)



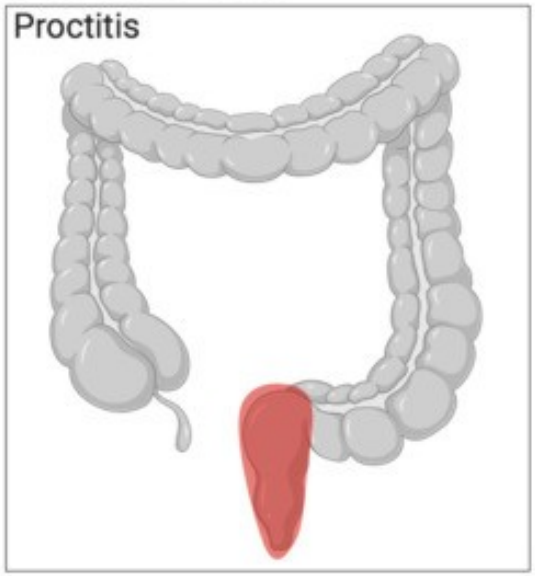


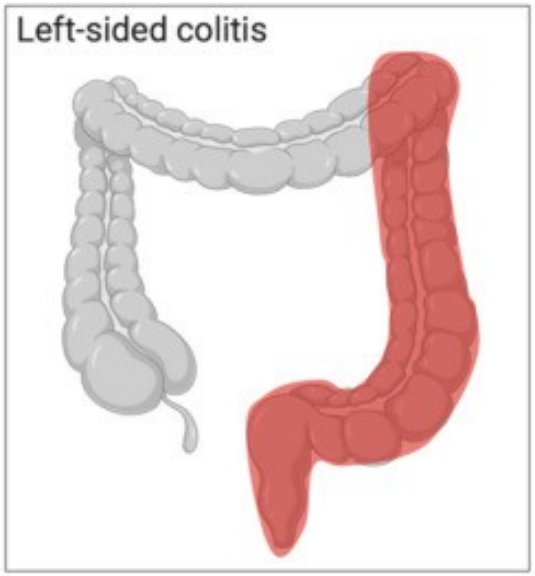
Crohn's Disease

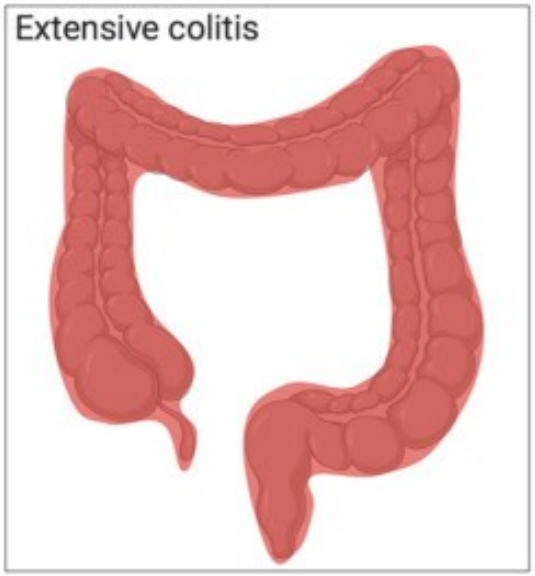
Ulcerative Colitis



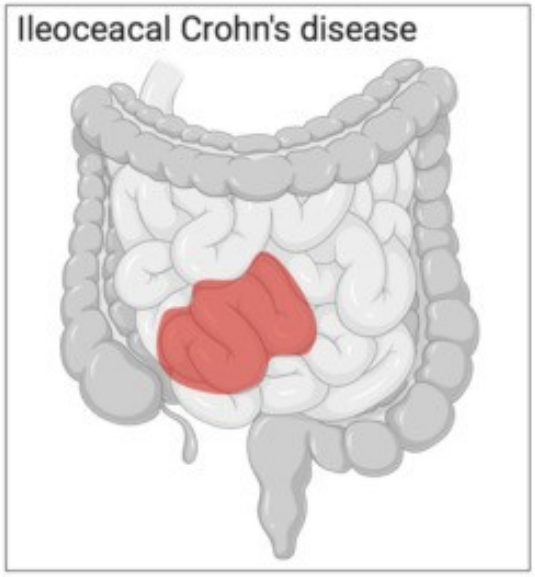
A) Ulcerative Colitis

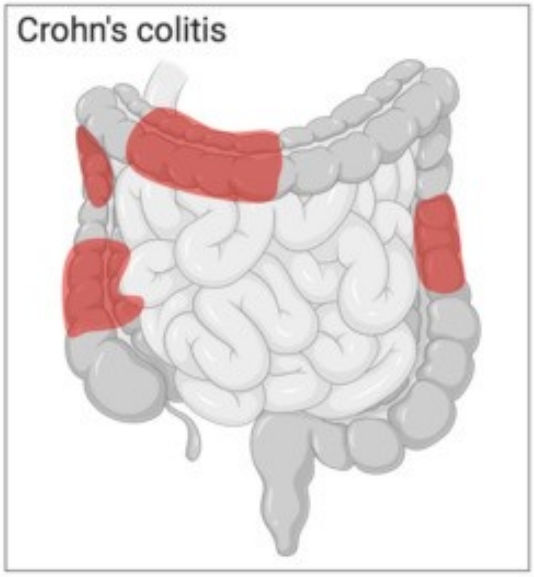


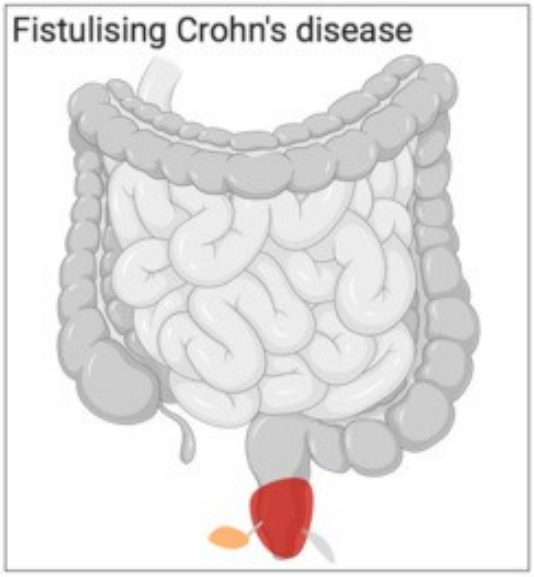




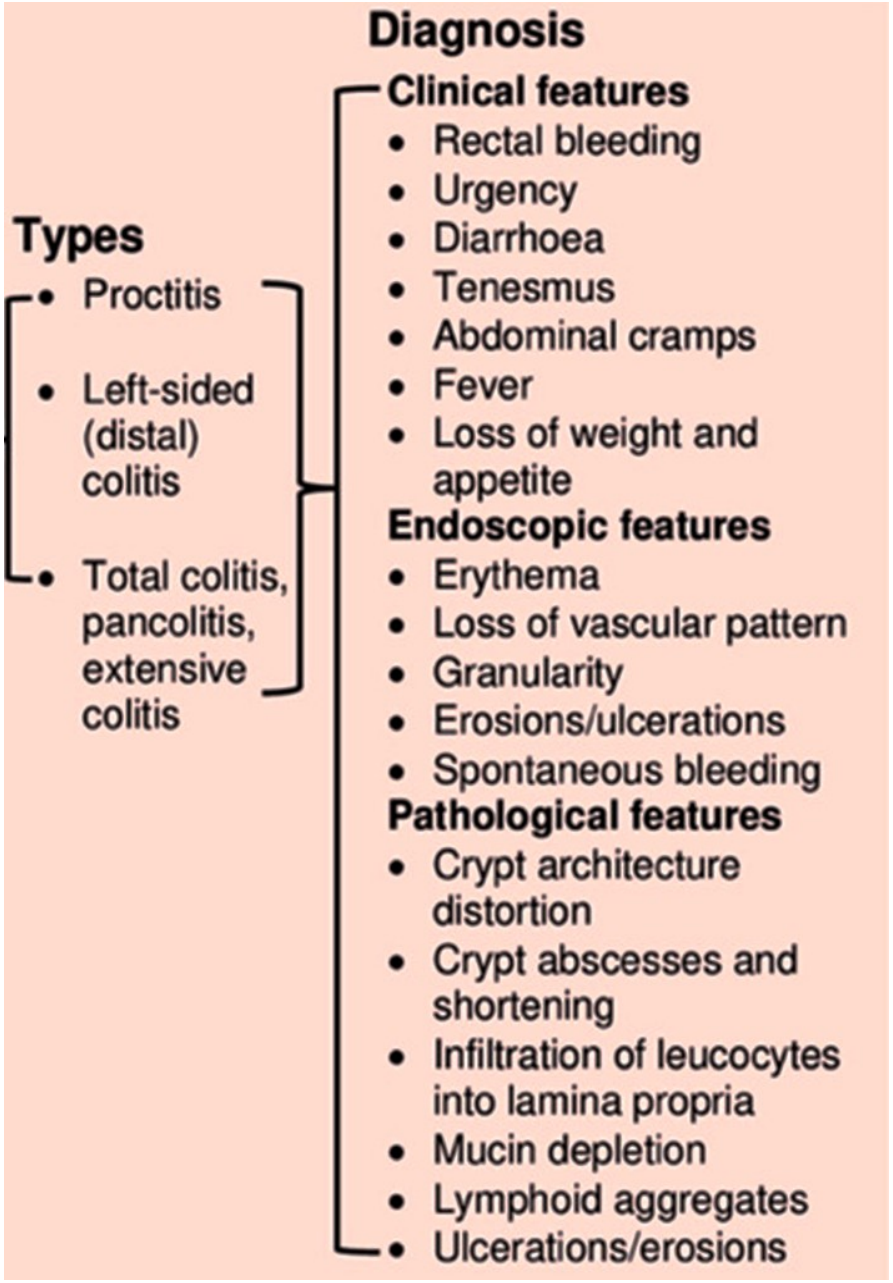
B) Crohn's Disease



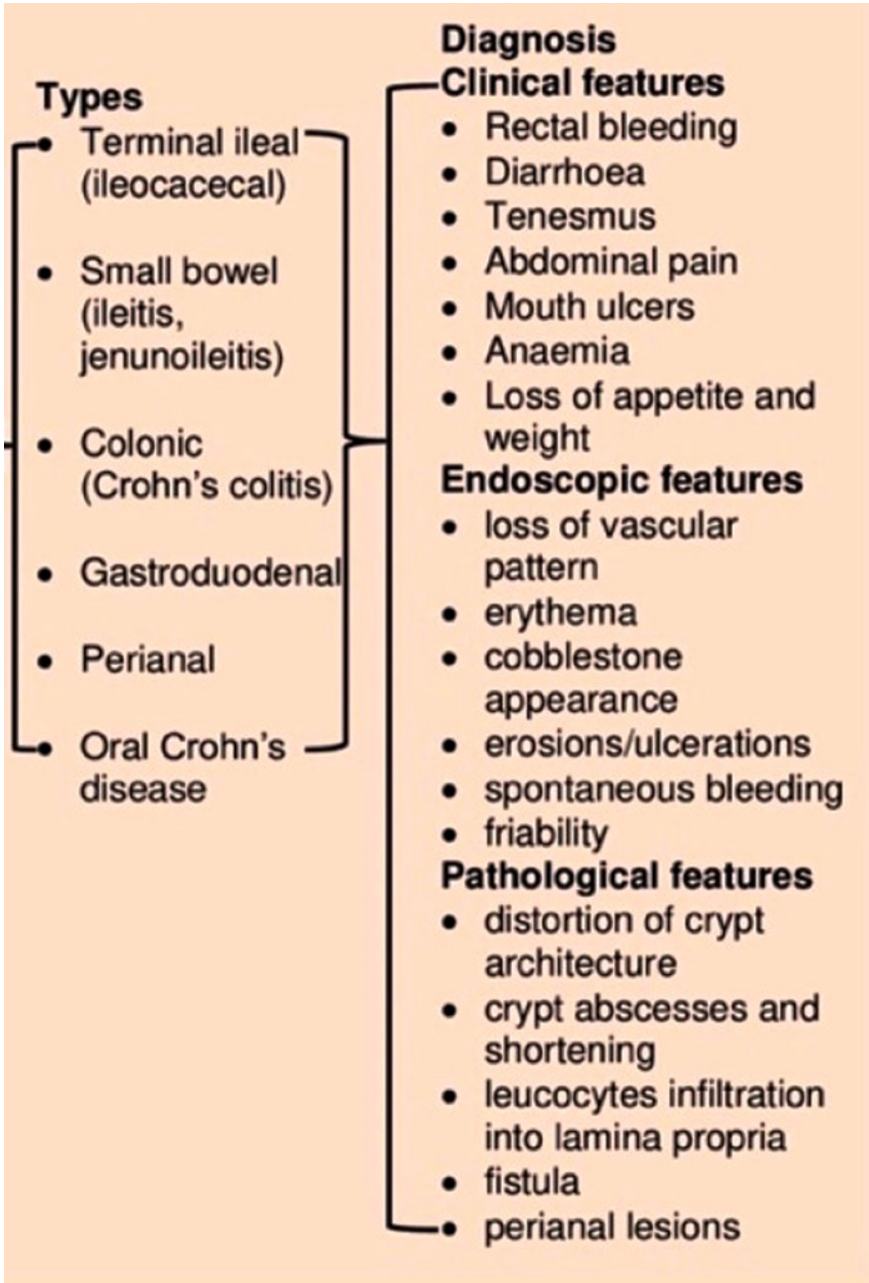




Ulcerative Colitis



Crohn disease



Indeterminate colitis (IC)

In about 5% to 10% of IBD cases the diagnosis is inconclusive

IC is a diagnosis reserved for **surgical specimens** from patients with **severe clinical disease requiring urgent colectomy**

Ambiguous histology that does not permit precise separation of CD from UC

Criteria of CD (fissuring and transmural inflammation) may be seen in **otherwise typical cases of UC**

Diagnostic uncertainty is usually an issue in **children**

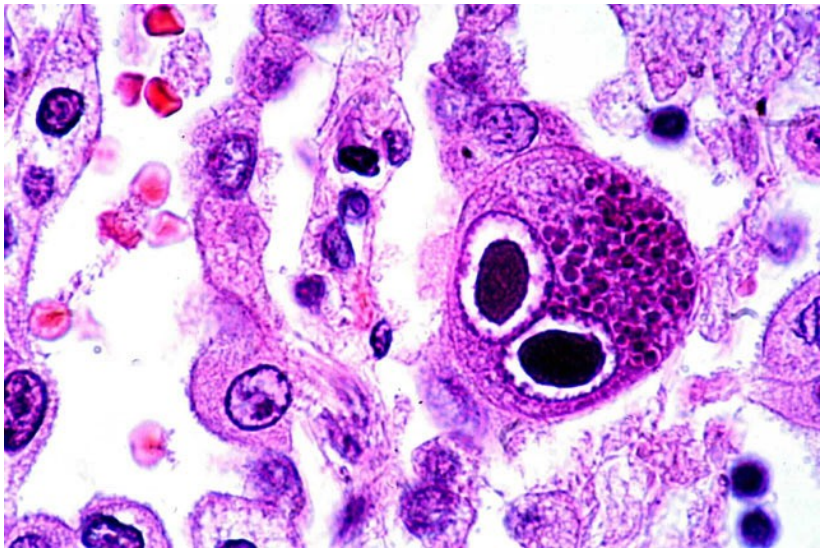
Causes of uncertainty in IBD classification	
UC may be confused for CD	**CD can have UC-like features**
1. Fulminant UC or toxic megacolon 2. Segmental disease (cecal or peri-appendiceal patch, effects of healing or therapy) 3. Rectal sparing often seen in children 4. Granulomas that are crypt related or secondary to superimposed infection 5. Involvement of the ileum (backwash, infection, drugs, bowel prep) 6. Upper GI involvement (rare)	1. CD with mucosal only (non-mural) disease 2. Rectal involvement only (~5 -10%) 3. Diffuse colonic disease

Causes of uncertainty in IBD are failure to recognize IBD mimics or failure to recognize diseases that may occur in patients with IBD	
IBD mimics	**Diseases that may occur with IBD**
Ischemic colitis Radiation colitis Microscopic colitis (atypical) Diverticular disease-associated colitis Infectious colitis (Yersinia, TB, LGV, other) Diversion colitis Drug-induced colitis (NSAIDs, Ipilimumab) Vasculitis (Behcet syndrome)	CMV Pseudomembranous colitis Ischemia Radiation Drugs Microscopic colitis (atypical) Other

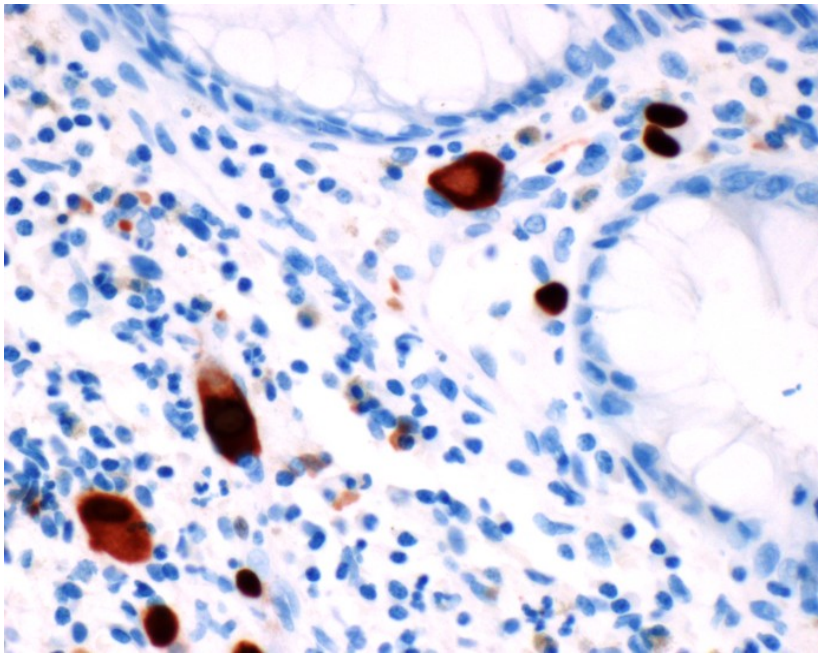
Treatment effects in IBD

May change distribution pattern and severity of inflammation (patchiness, rectal sparing, near normal histology)

Testing for CMV should be performed in patients with severe colitis refractory to immunosuppressive therapy



CMV colitis



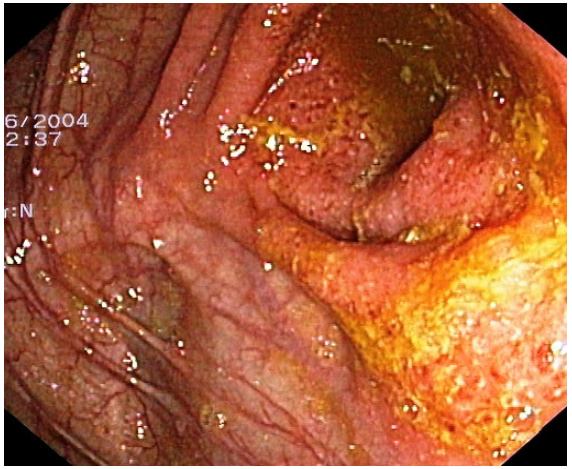
Cecal patch

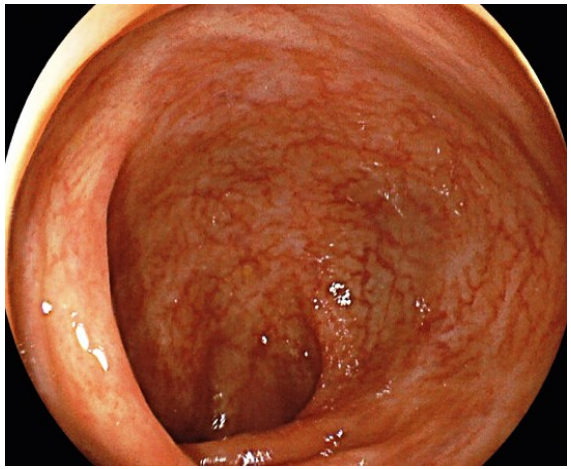
Discontinuous involvement of the cecum in patients with left-sided UC

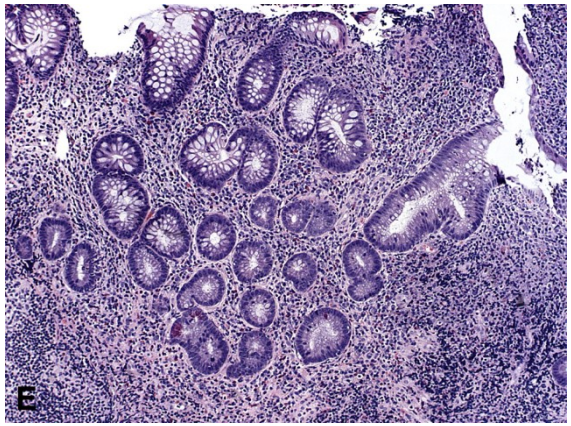
Prevalence of 5%

Clinically severe (rectal bleeding, diarrhea, and abdominal pain)

Cecal patch has **similar histology to the main lesion of UC**







IBD-like conditions/secondary IBD

Medications

Immunomodulators, anti-tumor necrosis factor alpha agents, anti-interleukin agents, interferons, immune stimulating agents and checkpoint inhibitors

Bowel altering surgeries

Colectomy can in some cases give rise to de novo CD, **pouchitis** of the ileal pouch or **post-colectomy enteritis syndrome**

Organ transplantation

Solid organ transplantation or hematopoietic stem cell transplantation stem cells with **GVH reaction**

Fecal microbiome

Fecal microbiota transplantation for treatment of recurrent *Clostridium difficile infection*

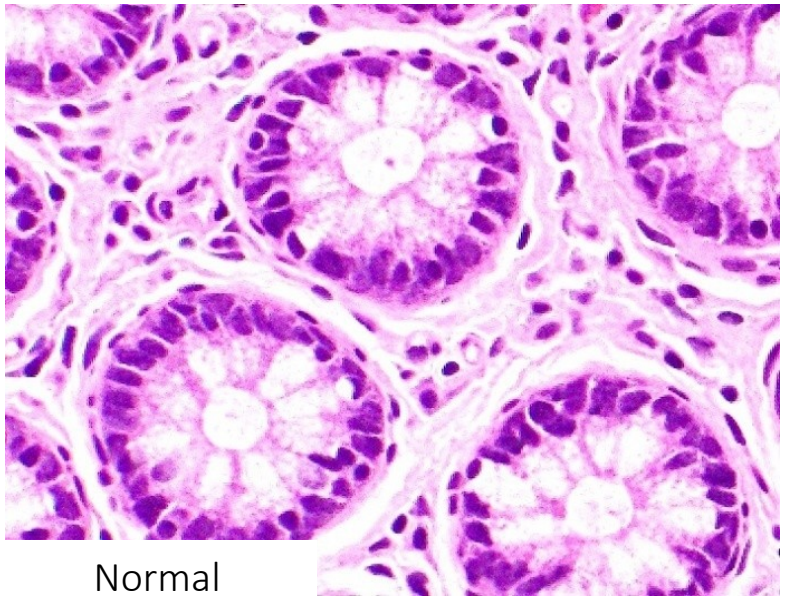
Inflammatory disease activity evaluation in IBD	
Grade of activity	**Description**
Inactive	No neutrophils
Mildly active	Active inflammation involving <50% of the mucosa with no crypt abscess
Moderately active	Active inflammation involving > 50% of the mucosa with crypt abscess
Severely active	Active inflammation with hemorrhage and surface erosion or ulceration

Dysplasia and carcinoma in IBD

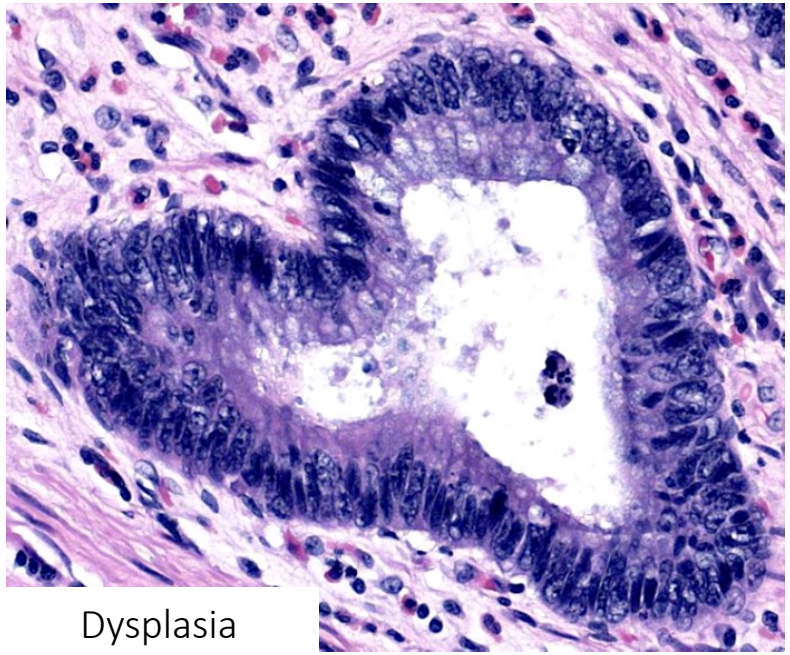
Dysplasia refers to disordered cellular growth with nuclear abnormality (nuclear enlargement and irregular chromatin)

Dysplasia in IBD can be flat or raised (villous or nodular)

Dysplasia is a precancerous lesion but only some progress to invasive carcinoma



Normal

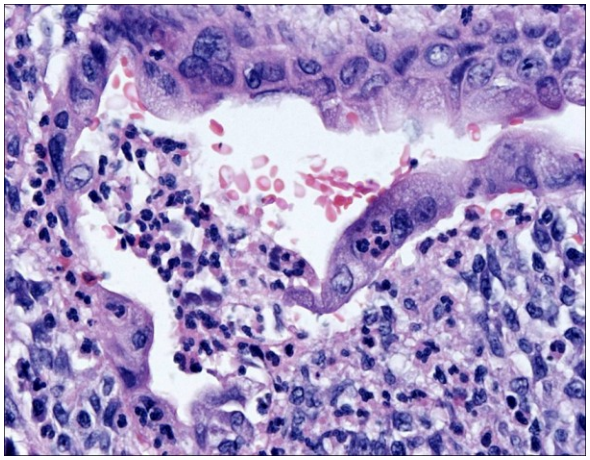


Dysplasia

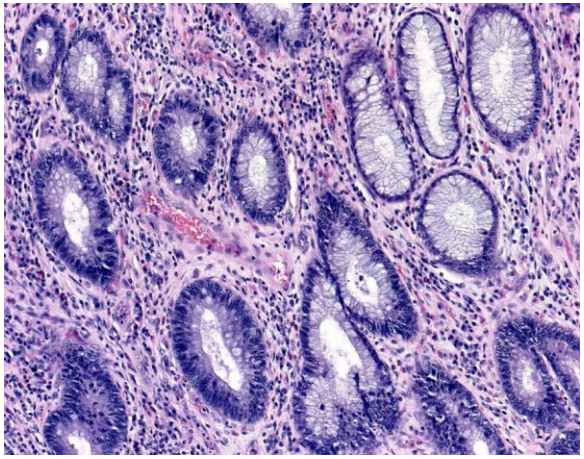
Dysplasia evaluation in IBD

Negative for dysplasia	No dysplasia present
Indefinite for dysplasia	No sure signs of dysplasia present
Low grade dysplasia	Mild nuclear abnormality limited to the basal half of the cell with no epithelial stratification or complex architecture
High grade dysplasia	Marked nuclear abnormality involving the luminal half of the epithelium with epithelial stratification and a complex architecture

Indefinite



LG



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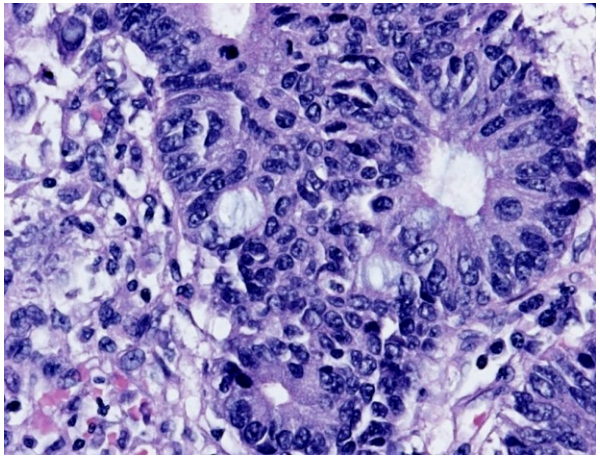


Dysplasia in IBD

Dysplasia grade
Negative
Indefinite
Low grade
High grade
Invasive carcinoma

Diagnosis and grade of dysplasia should be confirmed by an independent GI pathologist

Inter-observatory agreement, especially on the evaluation of indefinite and low-grade dysplasia is poor

Conventional dysplasias resemble sporadic colorectal adenomas
Non-conventional dysplasias can be intestinal, gastric or mixed

New dysplasia in IBD classification (2021)

Most dysplasias in IBD resembles sporadic colorectal adenomas morphologically (adenoma-like dysplasia) and are called conventional dysplasias

Other types of dysplasia in IBD have been described

A new classification system with 3 broad categories

- Intestinal dysplasia (conventional and non-conventional)
- Gastric dysplasia (foveolar, pyloric type, serrated)
- Mixed intestinal-gastric dysplasia

Intestinal dysplasia in IBD

Conventional (adenoma-like dysplasia)

- Tubular/tubulovillous/ villous dysplasia

Non-conventional

- hypermucinous
- Serrated
- Crypt cell type
- Paneth cell type
- Goblet cell deficient

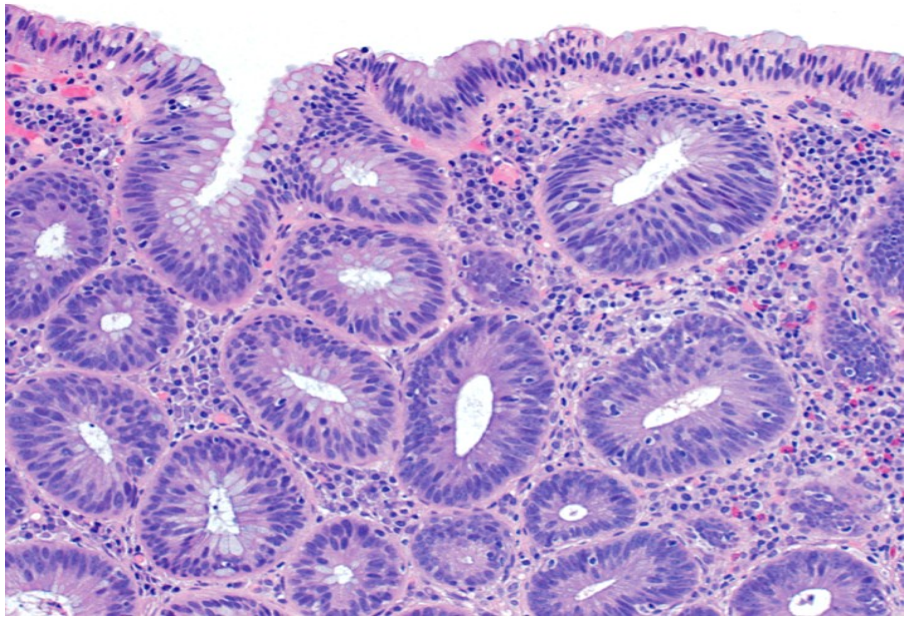
Table 2. Histological subtypes of inflammatory bowel disease-associated non-conventional dysplasia

Histological subtype	Microscopic features
Hypermucinous dysplasia	Tubulovillous/villous pattern Prominent intracytoplasmic mucin Degree of atypia increases from the tips of villi to the bases of crypts
Serrated dysplasia	Share morphological features with sporadic counterparts SSL-like, TSA-like and serrated dysplasia NOS-like subtypes
Crypt cell dysplasia	Flat, non-crowded, tubular pattern Non-stratified nuclei limited to the crypt base, without surface involvement Mild nuclear enlargement, hyperchromasia, and irregularity
Dysplasia with increased Paneth cell differentiation	Tubular lesions lined by enlarged, hyperchromatic and pencillate nuclei Increased Paneth cell differentiation The number of goblet cells may be reduced
Goblet cell-deficient dysplasia	Tubular lesions lined by enlarged, hyperchromatic and pencillate nuclei Complete or near-complete absence of goblet cells Scattered Paneth cells may be seen

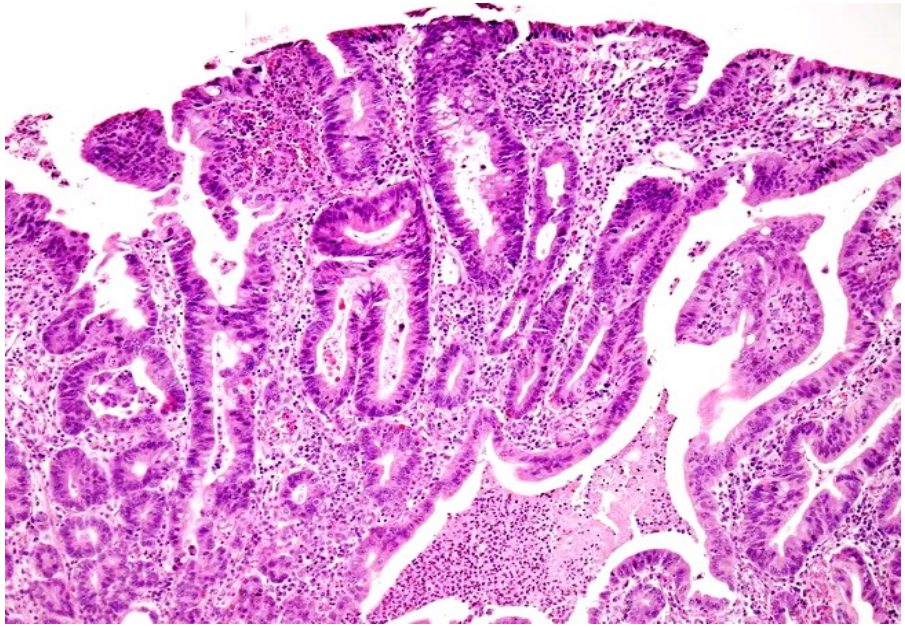
NOS, Not otherwise specified; SSL, Sessile serrated lesion; TSA, Traditional serrated adenoma.

Inter-observer agreement between some of the subgroups is poor

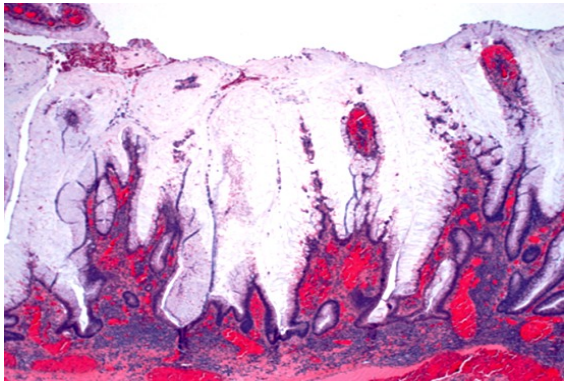
Conventional (adenoma-like) dysplasia in IBD



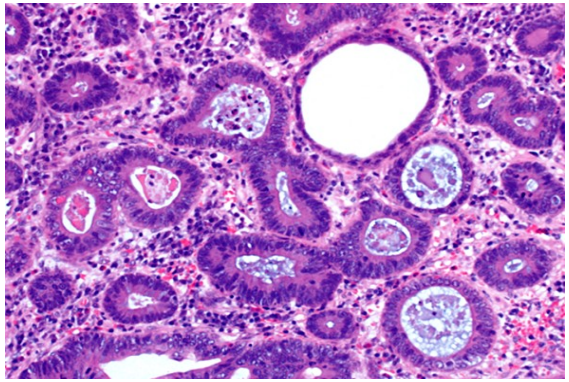
Low grade conventional dysplasia in IBD



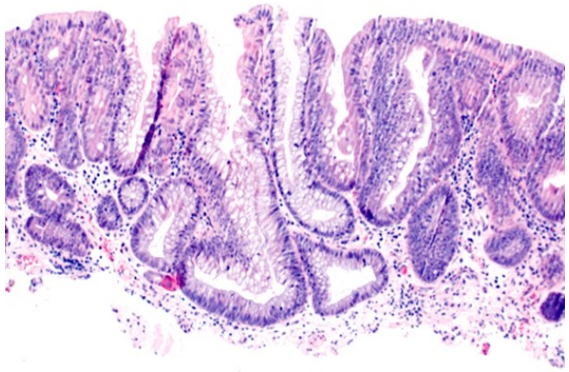
High grade conventional dysplasia in IBD



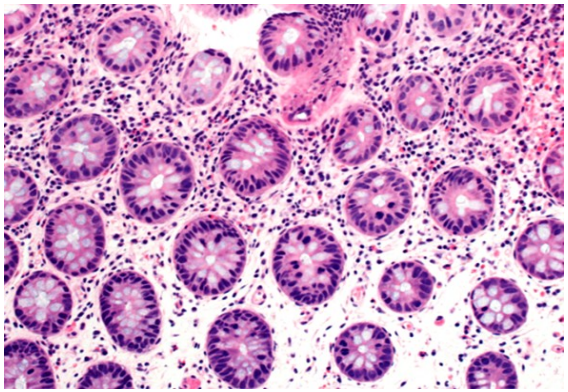
Hypermucinous dysplasia



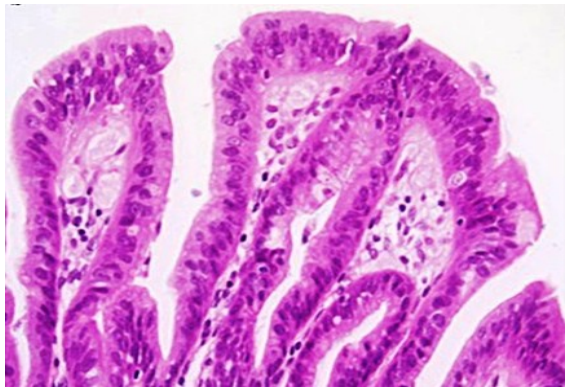
Goblet cell deficient dysplasia



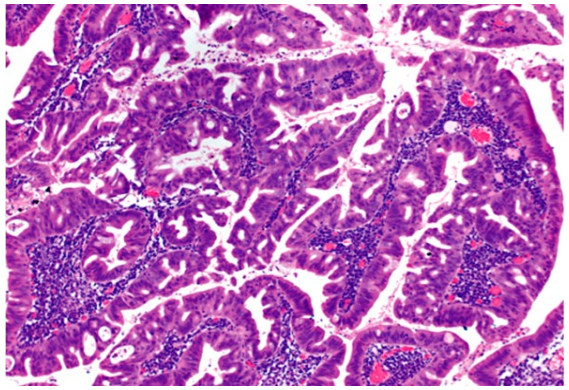
SSL-like dysplasia



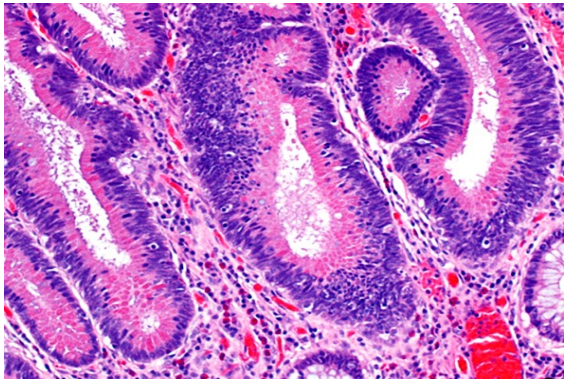
Crypt cell dysplasia



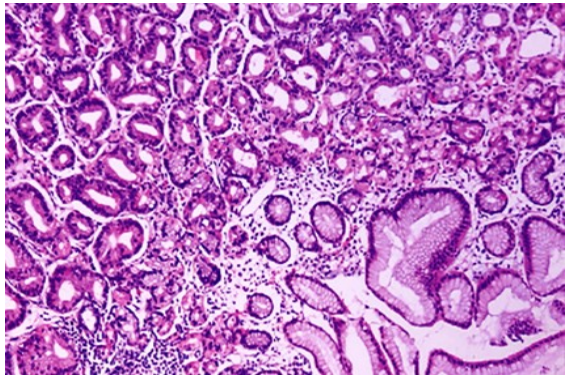
Gastric foveolar-type dysplasia



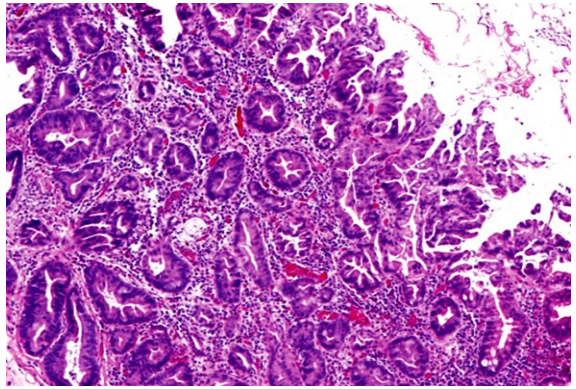
TSA-like dysplasia



Paneth cell rich dysplasia



Pyloric gland-like dysplasia

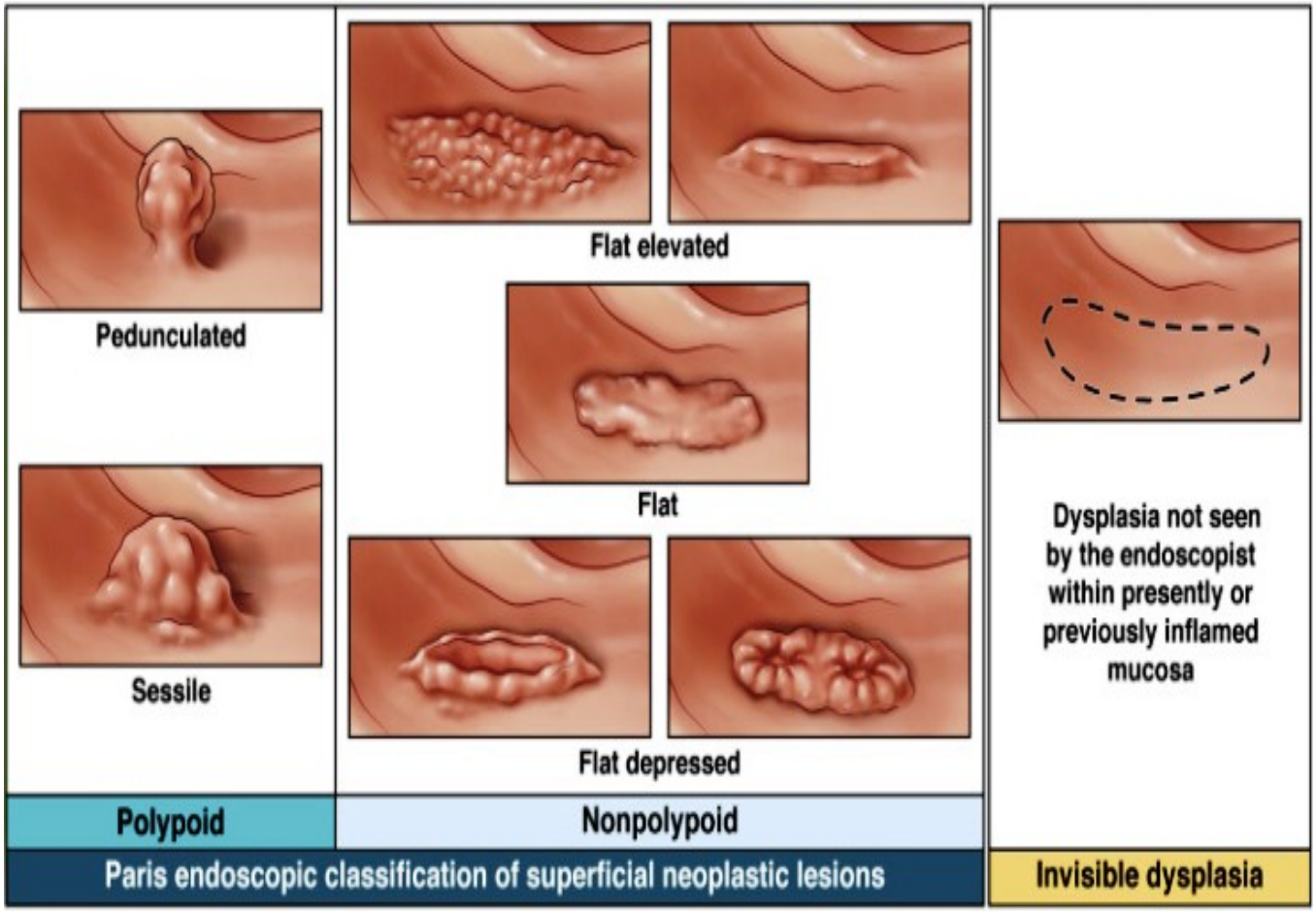


Serrated dysplasia NOS

Non-conventional dysplasia morphological, clinicopathological and molecular characteristics	
Hypermucinous dysplasia	2% of dysplasia KRA, p53 mutations Left colon Higher risk progression to HGD or CRC
Crypt cell dysplasia	4% of dysplasia KRA, p53 mutations Left colon Higher risk of progression to HGD or CRC
Goblet cell deficient dysplasia	3% of dysplasia KRA, p53, PIK3CA mutations Right or left colon Higher risk of progression to HGD or CRC
Paneth cell dysplasia	13% of dysplasia Aneuploidy Right colon Higher risk for HGD or CRC Similar risk to traditional dysplasia
Serrated dysplasia	3% of dysplasia BRAF, KRAS Left or right colon Higher risk for HGD or CRC Similar risk to traditional dysplasia

2015 International Consensus Recommendations on Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients (SCENIC)

- Visible dysplasia
  - Polypoid
    - Pedunculated
    - Sessile
  - Nonpolypoid
    - Superficial elevated
    - Flat
    - Depressed
  - General descriptors
    - Ulcerated
    - Border
      - Distinct border
      - Indistinct border
- Invisible dysplasia



In addition to Paris classification, report lesion size, morphology, border clarity, ulceration, location, if within area of colitis, completeness of resection, and any special techniques used to visualize.

DALM (Dysplasia-Associated Lesion or Mass); ALM (Adenoma-Like Mass)

Microscopic colitis
(lymphocytic colitis & collagenous colitis)

Mean age at diagnosis is **60 to 65 years**

Female predominance

Chronic watery, non-bloody diarrhea and abdominal pain, fecal urgency, incontinence and weight loss

Normal endoscopy (mostly)

Diagnosis relies on **microscopic examination**

Risk factors include **medications** (NSAID and PPI use), and **autoimmune disorders** (Celiac disease, rheumatoid arthritis, thyroiditis)

Lymphocytic Colitis

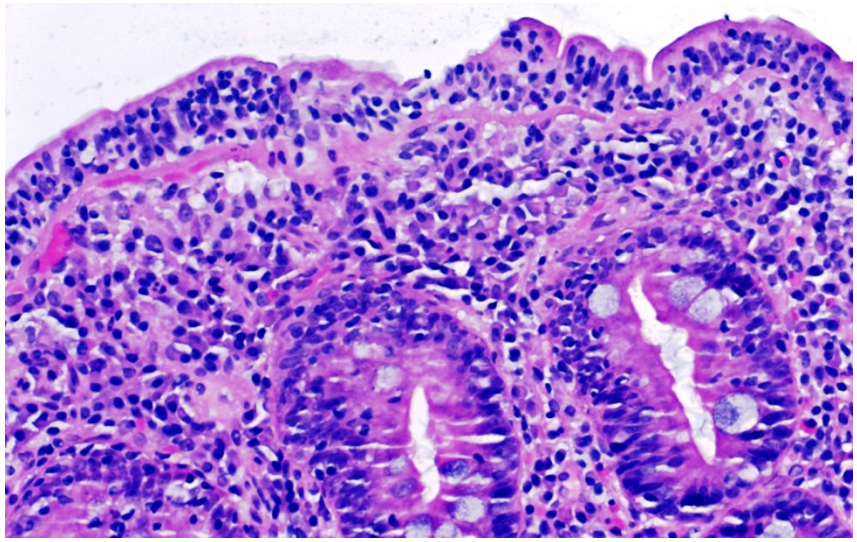
Intraepithelial lymphocytosis is the most prominent histological feature of lymphocytic colitis

At least 20 lymphocytes should be present per 100 epithelial cells

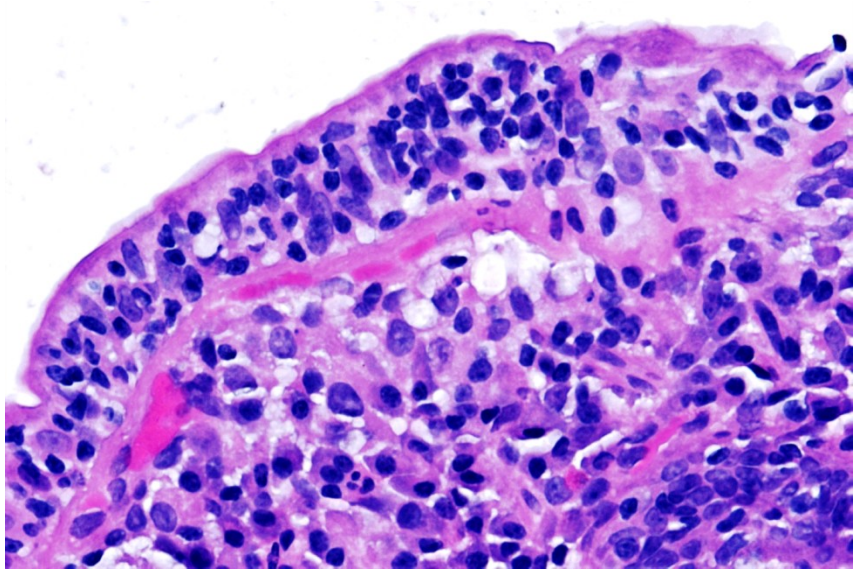
Surface epithelium shows evidence of injury and there is mucus depletion and reactive changes

Lamina propria is also expanded by a chronic inflammatory cell population containing prominent plasma cells

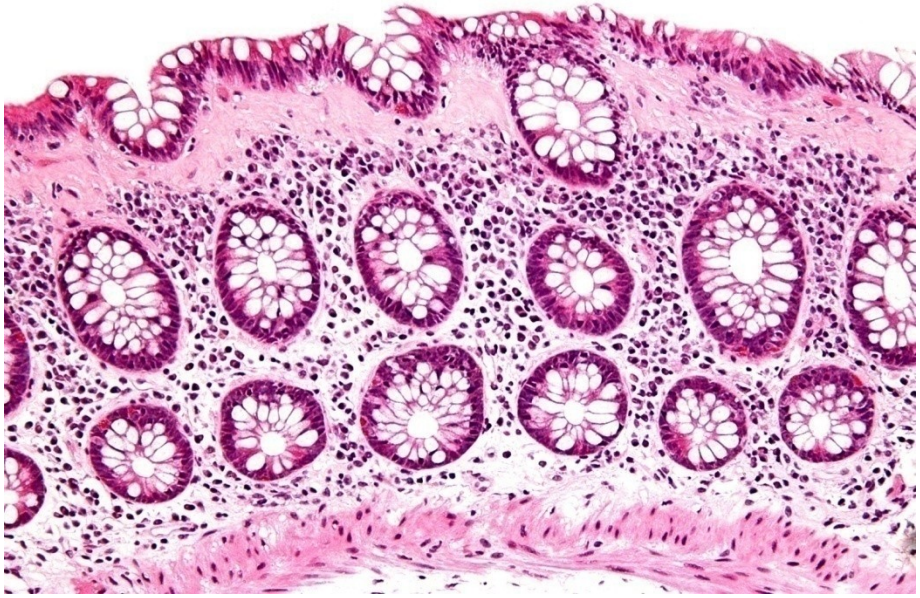
Differential diagnosis includes changes due to **bowel preparation, acute colitis, IBD, drug-induced colitis (Olmesartan)**



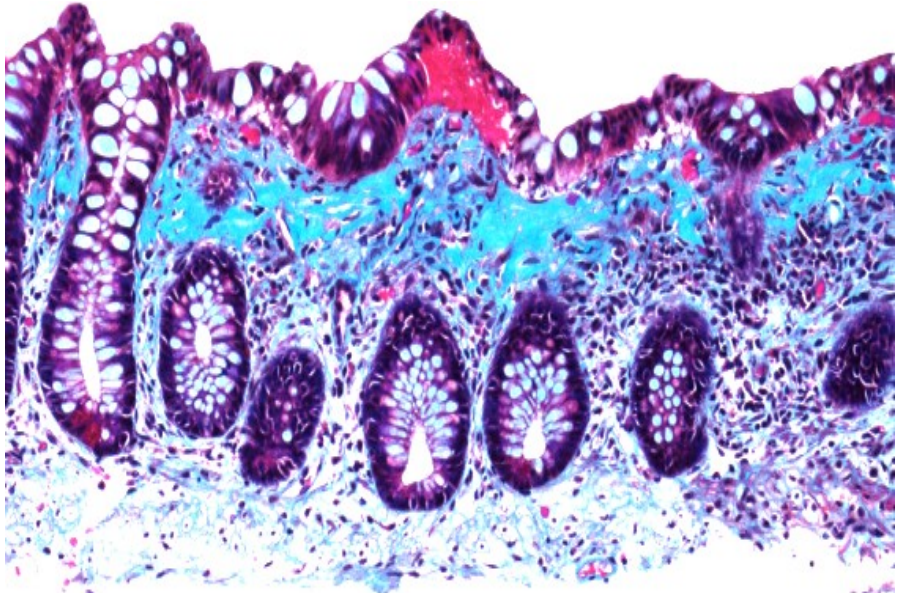
Lymphocytic colitis



Lymphocytic colitis



Collagenous colitis (H&E)



Collagenous colitis (Mason Trichrome)

Collagenous colitis

Collagenous colitis share common symptomatology with lymphocytic colitis

Thickened subepithelial collagen band (>10 µm vs <5 µm for normal) is the most important histological feature of collagenous colitis

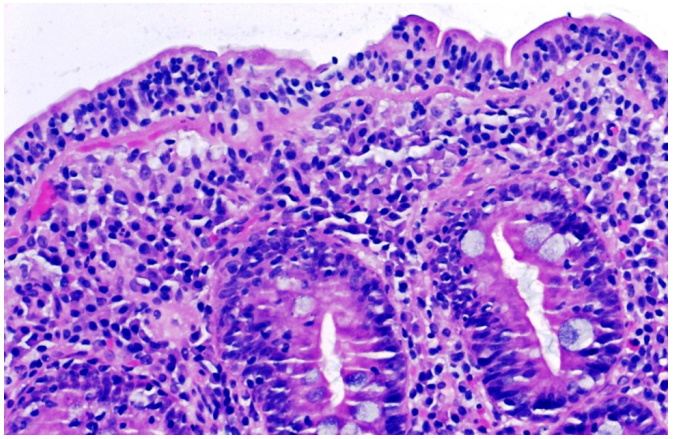
Irregular, "ragged" appearance of the collagen, with small tendrils creeping down into the superficial lamina propria with entrapment of capillaries, erythrocytes or inflammatory cells)

Intraepithelial lymphocytes are increased but not as dramatically

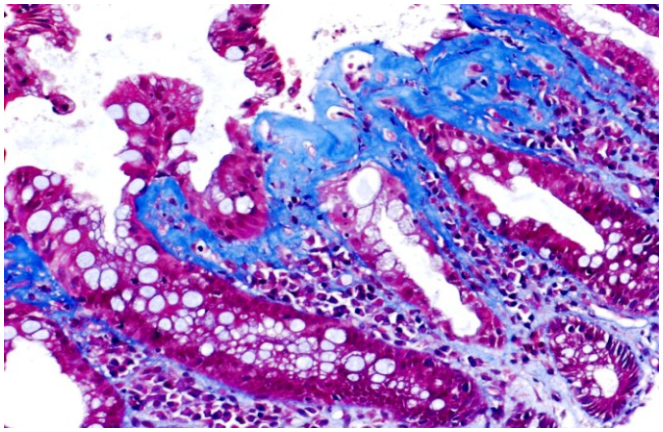
Epithelial layer damage and lamina propria expansion with a chronic inflammatory infiltrate may be seen

Eosinophils may also be prominent

Normal large bowel mucosa



Lymphocytic colitis



Collagenous colitis

Microscopic colitis has been associated with certain medications (NSAIDs, PPIs, ranitidine, ticlopidine and flutamide)

Progression of lymphocytic colitis to collagenous colitis has been described

Lymphocytic colitis and collagenous colitis appear to represent **different morphological phases of one disease state** and may share a **common immune-mediated etiology and pathogenesis**

Aberrant histology in lymphocytic and collagenous colitis

Variations in histology from classic lymphocytic or collagenous colitis to IBD-like changes have been described

IBD like changes seen in aberrant microscopic colitis

- Cryptitis 30%
- Paneth cell metaplasia 30%
- Ulceration 2%
- Architectural abnormalities 5%

Histology does not correlate with symptoms, results of medical treatment or outcome

Spontaneous resolutions of collagenous colitis and lymphocytic colitis have occurred

Oral corticosteroid can be an effective treatment

Infectious colitides

Common bacterial agents

Campylobacter species, Salmonella species, Shigella species, Escherichia coli, Staphylococcus aureus, Neisseria gonorrhoeae, Treponema pallidum, Yersinia species, Clostridioides difficile, and Mycobacterium species

E. coli pathogens (six major categories recognized)

Enterohemorrhagic E. coli (EHEC), Enterotoxigenic (ETEC), Enteroinvasive (EIEC), Enteropathogenic (EPEC), Enteroaggregative (EAEC) and Diffusely adherent (DAEC)

Viral agents

Norwalk agent and rotavirus, CMV and HSV, HIV

Other infectious agents

Fungi and parasites

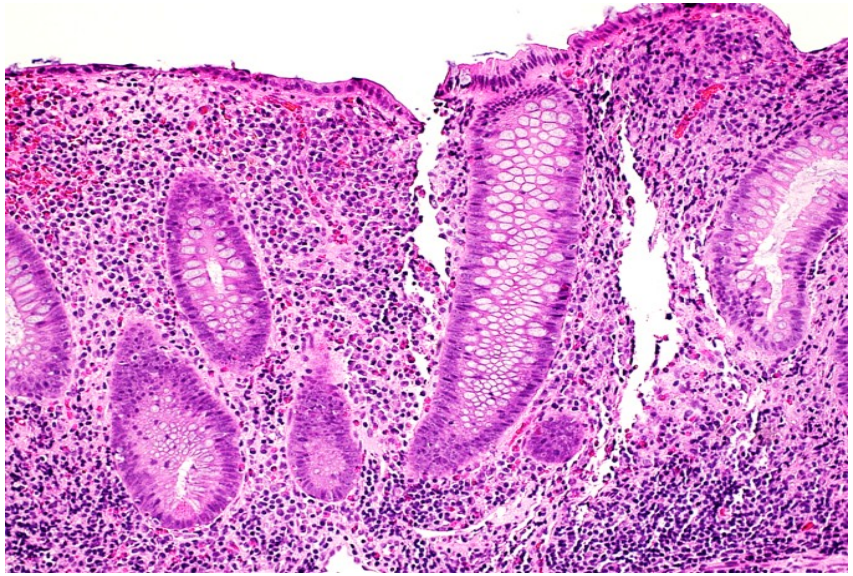
Mechanisms in infectious colitis pathogenesis

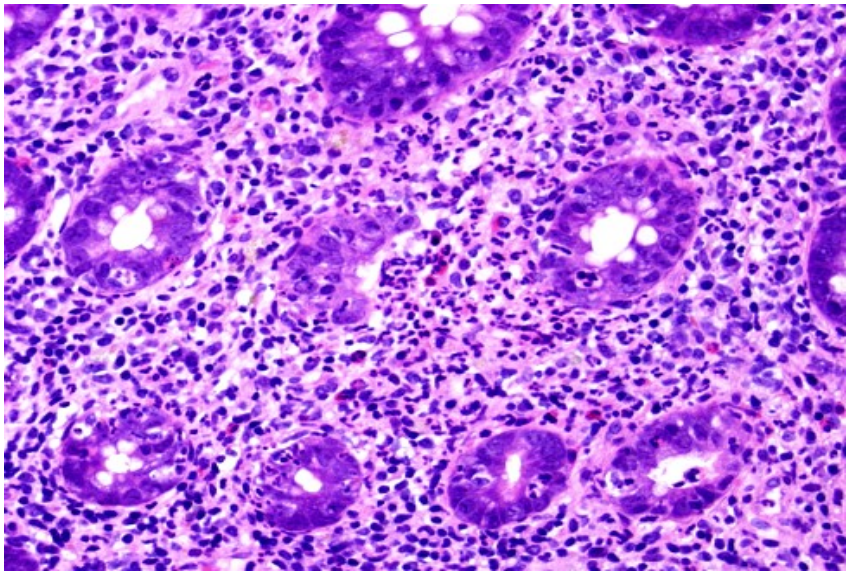
1. **Bacterial adhesion, invasion and epithelial cell damage**
   Salmonella, Campylobacter jejuni, Shigella, or enteroinvasive Escherichia coli (EIEC)

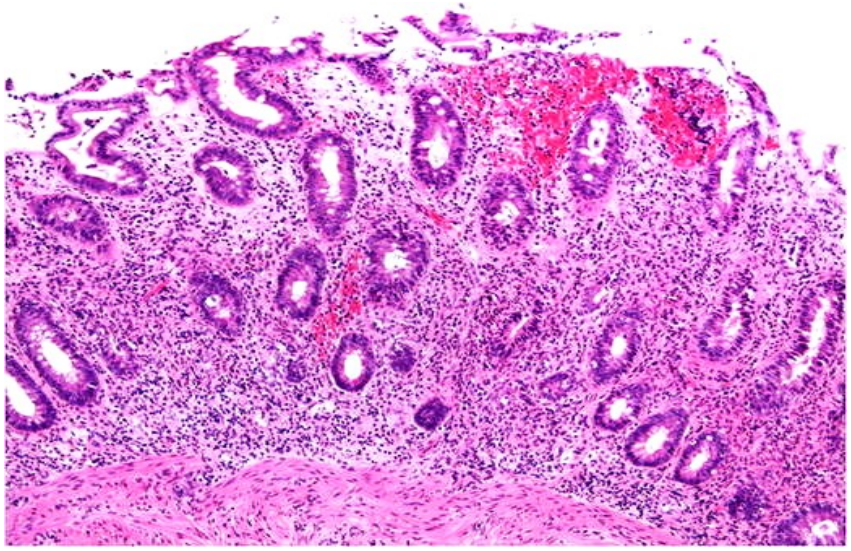
2. **Toxin production**
   Clostridioides difficile

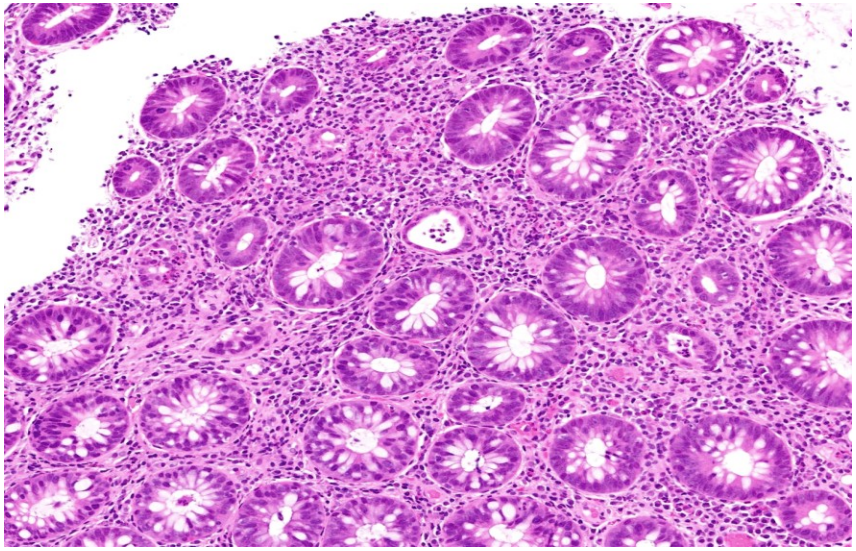
3. **Immune cell activation**
   Triggers an immune response by activating immune cells (release pro-inflammatory cytokines TNF-alpha, IL-1beta)

4. **Microflora disruption**
   Clostridioides difficile









Self-limited colitis (infectious diarrhea)

Clostridioides difficile colitis (Pseudomembranous colitis)

C difficile is a **toxin-producing gram-positive, anaerobic bacterium**

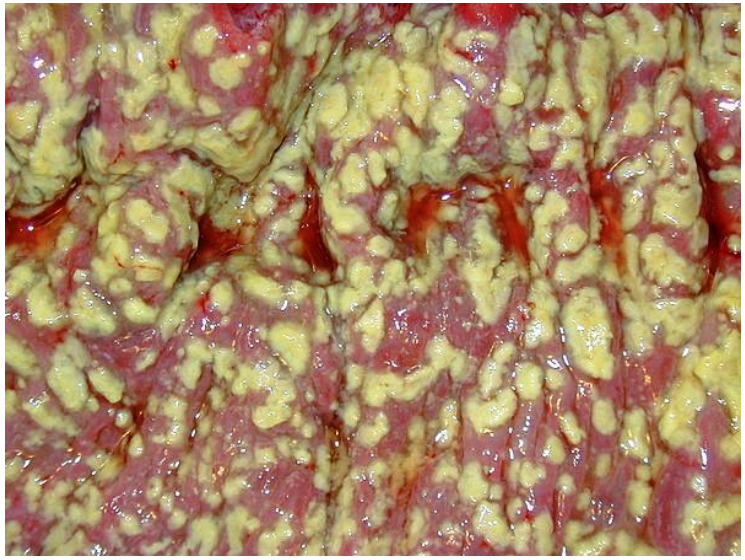
Major cause of **health care–associated infection**

C. difficile is **normally found** in the large intestine of humans

Pathogenicity relies on the presence of **toxigenic strains** (TcdA and TcdB)

Patients at highest risk are **hospitalized patients older than 65 years with recent antibiotic exposure**

Antibiotics changes the fecal microbiome that allow **expansion of the C. difficile** population and ultimately, **uninhibited toxin production**



Findings at endoscopy
Elevated yellow-white plaque on the mucosal surface of the colon forming pseudomembrane

Some early lesions resemble **aphthous ulcers** of CD

Pseudomembranous colitis

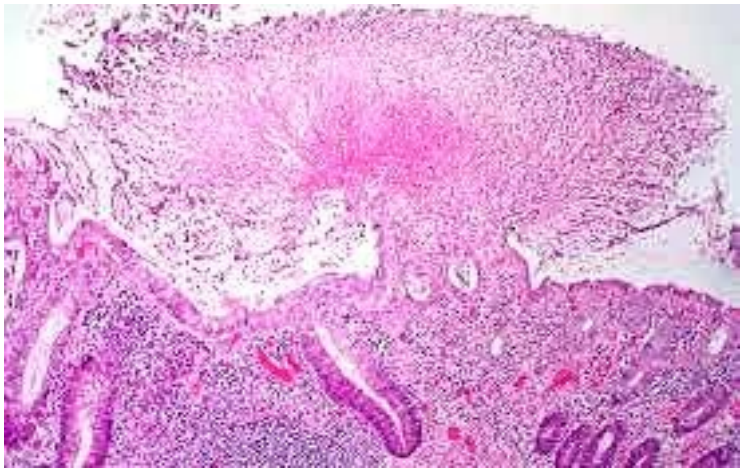
Patchy necrosis of the superficial portions of the colonic mucosa

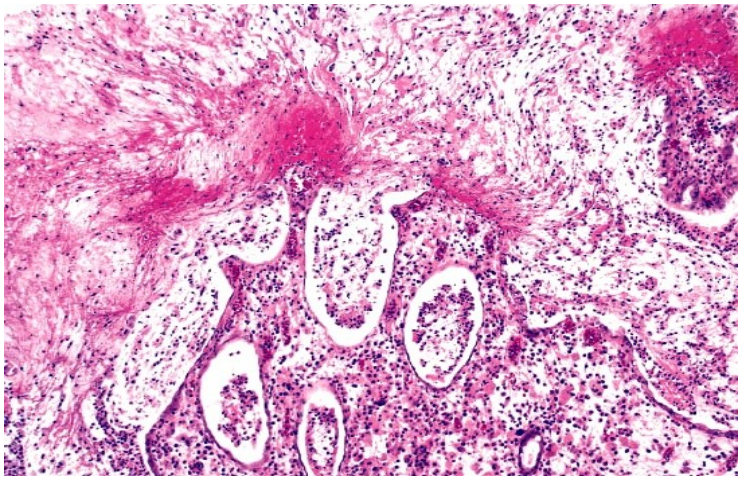
Crypt dilatation

Inflammatory pseudomembrane (fibrin, pus, and mucus exudes) from the superficial aspects of the degenerating crypts in mushroom-like configuration

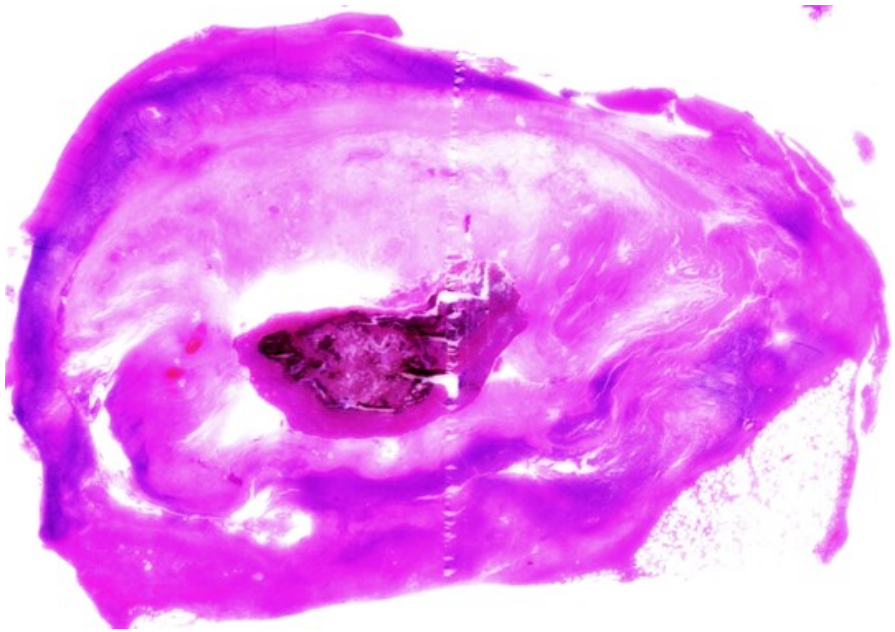
With progression (confluent plaques and crypt necrosis) the lesion become **indistinguishable from ischemic colitis**

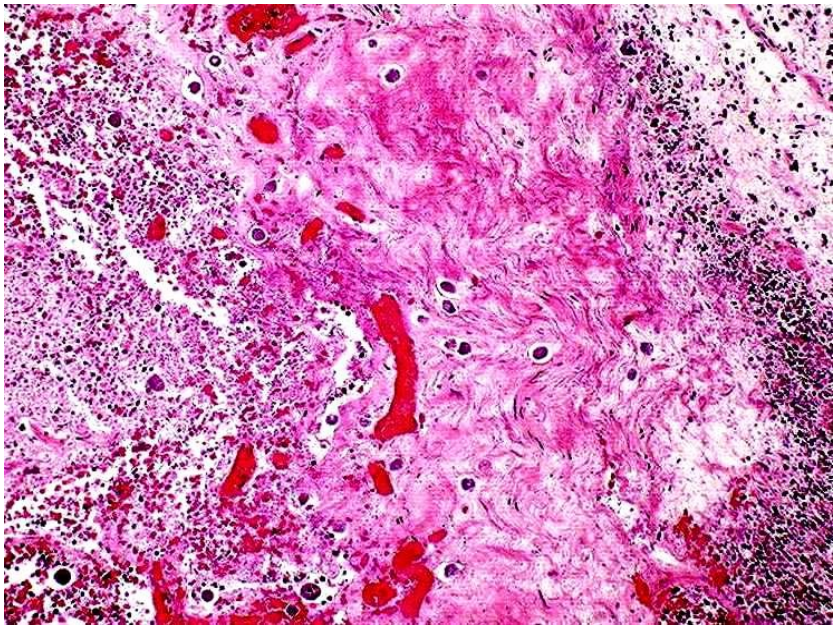
Colonic paralysis with toxic megacolon and subsequent perforation can occur

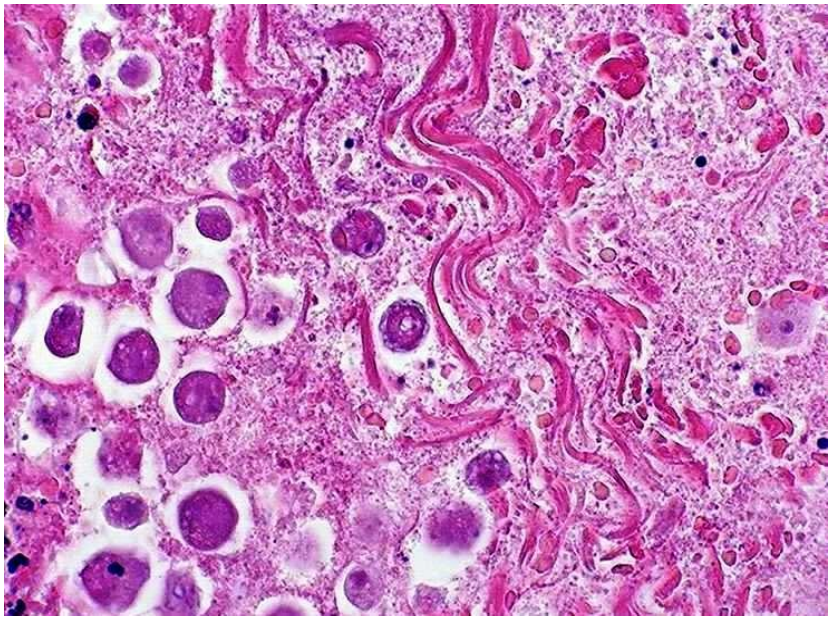




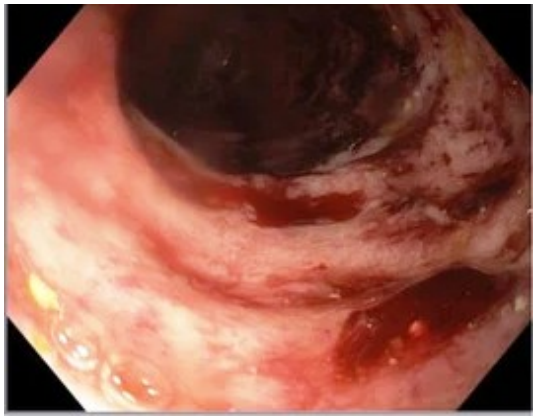
Amebic appendicitis (Entamoeba histolytica appendicitis)

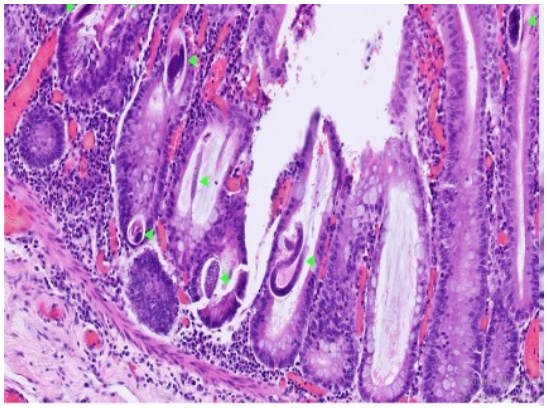


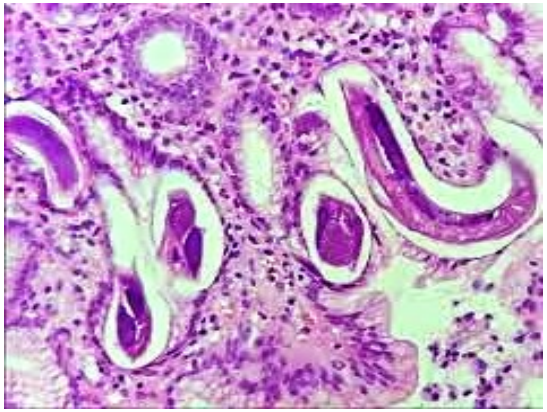




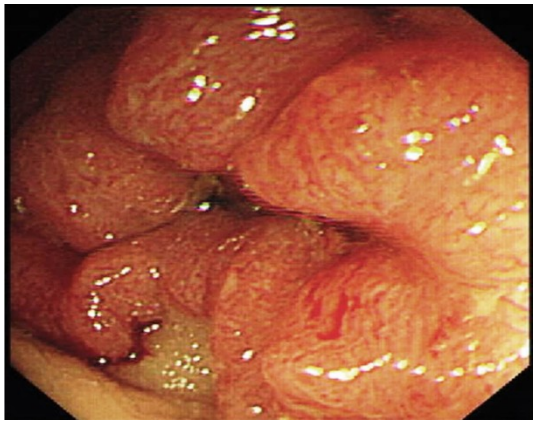
Strongyloides stercoralis colitis

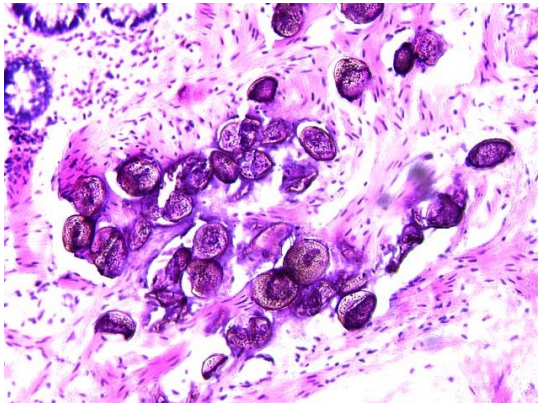






Intestinal schistosomiasis





Pathological evaluation of the inflammatory diseases of the colorectum

Presence or absence of colitis

Inflammatory cells, ulceration, hemorrhage, granuloma

Site of inflammation

Lamina propria, epithelium (surface , crypt)

Duration of disease

Acute (normal architecture, neutrophilic infiltrate)

Chronic (distorted architecture, lymphocytes, plasma cells, granuloma)

Grade of activity (mild, moderate, severe)

Density of inflammatory infiltrate, hemorrhage, ulceration

Extent of disease

Focal, diffuse, mucosal, transmural

Etiology

Idiopathic, infective, ischemic, etc